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# NOVEL NUCLEIC ACIDS AND POLYPEPTIDES

#### 1. TECHNICAL FIELD

The present invention provides novel polynucleotides and proteins encoded by such polynucleotides, along with uses for these polynucleotides and proteins, for example in therapeutic, diagnostic and research methods.

#### 2. BACKGROUND

Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs, chemokines, and interleukins) has matured rapidly over the past decade. The now routine hybridization cloning and expression cloning techniques clone novel polynucleotides "directly" in the sense that they rely on information directly related to the discovered protein (i.e., partial DNA/amino acid sequence of the protein in the case of hybridization cloning; activity of the protein in the case of expression cloning). More recent "indirect" cloning techniques such as signal sequence cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader sequence motif, as well as various PCR-based or low stringency hybridization-based cloning techniques, have advanced the state of the art by making available large numbers of DNA/amino acid sequences for proteins that are known to have biological activity, for example, by virtue of their secreted nature in the case of leader sequence cloning, by virtue of their cell or tissue source in the case of PCR-based techniques, or by virtue of structural similarity to other genes of known biological activity.

Identified polynucleotide and polypeptide sequences have numerous applications in, for example, diagnostics, forensics, gene mapping; identification of mutations responsible for genetic disorders or other traits, to assess biodiversity, and to produce many other types of data and products dependent on DNA and amino acid sequences.

#### 3. SUMMARY OF THE INVENTION

The compositions of the present invention include novel isolated polypeptides, novel isolated polynucleotides encoding such polypeptides, including recombinant DNA molecules, cloned genes or degenerate variants thereof, especially naturally occurring variants such as allelic variants, antisense polynucleotide molecules, and antibodies that specifically recognize one or more epitopes present on such polypeptides, as well as hybridomas producing such antibodies.

The compositions of the present invention additionally include vectors, including expression vectors, containing the polynucleotides of the invention, cells genetically engineered to contain such polynucleotides and cells genetically engineered to express such polynucleotides.

The present invention relates to a collection or library of at least one novel nucleic acid sequence assembled from expressed sequence tags (ESTs) isolated mainly by sequencing by hybridization (SBH), and in some cases, sequences obtained from one or more public databases. The invention relates also to the proteins encoded by such polynucleotides, along with therapeutic, diagnostic and research utilities for these polynucleotides and proteins. These nucleic acid sequences are designated as SEQ ID NO: 1-236 and 473-708. The polypeptides sequences are designated SEQ ID NO: 237-472 and 709-944. The nucleic acids and polypeptides are provided in the Sequence Listing. In the nucleic acids provided in the Sequence Listing, A is adenosine; C is cytosine; G is guanine; T is thymine; and N is any of the four bases. In the amino acids provided in the Sequence Listing, \* corresponds to the stop codon.

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The nucleic acid sequences of the present invention also include, nucleic acid sequences that hybridize to the complement of SEQ ID NO: 1-236 and 473-708 under stringent hybridization conditions; nucleic acid sequences which are allelic variants or species homologues of any of the nucleic acid sequences recited above, or nucleic acid sequences that encode a peptide comprising a specific domain or truncation of the peptides encoded by SEQ ID NO: 1-236 and 473-708. A polynucleotide comprising a nucleotide sequence having at least 90% identity to an identifying sequence of SEQ ID NO: 1-236 and 473-708 or a degenerate variant or fragment thereof. The identifying sequence can be 100 base pairs in length.

The nucleic acid sequences of the present invention also include the sequence information from the nucleic acid sequences of SEQ ID NO:1-236 and 473-708. The sequence information can be a segment of any one of SEQ ID NO:1-236 and 473-708 that uniquely identifies or represents the sequence information of SEQ ID NO:1-236 and 473-708.

A collection as used in this application can be a collection of only one polynucleotide. The collection of sequence information or identifying information of each sequence can be provided on a nucleic acid array. In one embodiment, segments of sequence information is provided on a nucleic acid array to detect the polynucleotide that contains the segment. The array can be designed to detect full-match or mismatch to the polynucleotide that contains the segment. The collection can also be provided in a computer-readable format.

This invention also includes the reverse or direct complement of any of the nucleic acid sequences recited above; cloning or expression vectors containing the nucleic acid sequences; and host cells or organisms transformed with these expression vectors. Nucleic acid sequences (or their reverse or direct complements) according to the invention have numerous applications in a variety of techniques known to those skilled in the art of molecular biology, such as use as hybridization probes, use as primers for PCR, use in an array, use in computer-readable media, use in sequencing

full-length genes, use for chromosome and gene mapping, use in the recombinant production of protein, and use in the generation of anti-sense DNA or RNA, their chemical analogs and the like.

In a preferred embodiment, the nucleic acid sequences of SEQ ID NO:1-236 and 473-708 or novel segments or parts of the nucleic acids of the invention are used as primers in expression assays that are well known in the art. In a particularly preferred embodiment, the nucleic acid sequences of SEQ ID NO:1-236 and 473-708 or novel segments or parts of the nucleic acids provided herein are used in diagnostics for identifying expressed genes or, as well known in the art and exemplified by Vollrath et al., Science 258:52-59 (1992), as expressed sequence tags for physical mapping of the human genome.

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The isolated polynucleotides of the invention include, but are not limited to, a polynucleotide comprising any one of the nucleotide sequences set forth in SEQ ID NO:1-236 and 473-708; a polynucleotide comprising any of the full length protein coding sequences of SEQ ID NO:1-236 and 473-708; and a polynucleotide comprising any of the nucleotide sequences of the mature protein coding sequences of SEQ ID NO:1-236 and 473-708. The polynucleotides of the present invention also include, but are not limited to, a polynucleotide that hybridizes under stringent hybridization conditions to (a) the complement of any one of the nucleotide sequences set forth in SEQ ID NO:1-236 and 473-708; (b) a nucleotide sequence encoding any one of the amino acid sequences set forth in the Sequence Listing; (c) a polynucleotide which is an allelic variant of any polynucleotides recited above; (d) a polynucleotide which encodes a species homolog (e.g. orthologs) of any of the proteins recited above; or (e) a polynucleotide that encodes a polypeptide comprising a specific domain or truncation of any of the polypeptides comprising an amino acid sequence set forth in the Sequence Listing.

The isolated polypeptides of the invention include, but are not limited to, a polypeptide comprising any of the amino acid sequences set forth in SEQ ID NO:237 – 472 or 709-944; or the corresponding full length or mature protein. Polypeptides of the invention also include polypeptides with biological activity that are encoded by (a) any of the polynucleotides having a nucleotide sequence set forth in SEQ ID NO:1-236 and 473-708; or (b) polynucleotides that hybridize to the complement of the polynucleotides of (a) under stringent hybridization conditions. Biologically or immunologically active variants of any of the polypeptide sequences in the Sequence Listing, and "substantial equivalents" thereof (e.g., with at least about 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or 99% amino acid sequence identity) that preferably retain biological activity are also contemplated. The polypeptides of the invention may be wholly or partially chemically synthesized but are preferably produced by recombinant means using the genetically engineered cells (e.g. host cells) of the invention.

The invention also provides compositions comprising a polypeptide of the invention. Polypeptide compositions of the invention may further comprise an acceptable carrier, such as a hydrophilic, e.g., pharmaceutically acceptable, carrier.

The invention also provides host cells transformed or transfected with a polynucleotide of the invention.

The invention also relates to methods for producing a polypeptide of the invention comprising growing a culture of the host cells of the invention in a suitable culture medium under conditions permitting expression of the desired polypeptide, and purifying the polypeptide from the culture or from the host cells. Preferred embodiments include those in which the protein produced by such process is a mature form of the protein.

Polynucleotides according to the invention have numerous applications in a variety of techniques known to those skilled in the art of molecular biology. These techniques include use as hybridization probes, use as oligomers, or primers, for PCR, use for chromosome and gene mapping, use in the recombinant production of protein, and use in generation of anti-sense DNA or RNA, their chemical analogs and the like. For example, when the expression of an mRNA is largely restricted to a particular cell or tissue type, polynucleotides of the invention can be used as hybridization probes to detect the presence of the particular cell or tissue mRNA in a sample using, e.g., in situ hybridization.

In other exemplary embodiments, the polynucleotides are used in diagnostics as expressed sequence tags for identifying expressed genes or, as well known in the art and exemplified by Vollrath et al., Science 258:52-59 (1992), as expressed sequence tags for physical mapping of the human genome.

The polypeptides according to the invention can be used in a variety of conventional procedures and methods that are currently applied to other proteins. For example, a polypeptide of the invention can be used to generate an antibody that specifically binds the polypeptide. Such antibodies, particularly monoclonal antibodies, are useful for detecting or quantitating the polypeptide in tissue. The polypeptides of the invention can also be used as molecular weight markers, and as a food supplement.

Methods are also provided for preventing, treating, or ameliorating a medical condition which comprises the step of administering to a mammalian subject a therapeutically effective amount of a composition comprising a polypeptide of the present invention and a pharmaceutically acceptable carrier.

In particular, the polypeptides and polynucleotides of the invention can be utilized, for example, in methods for the prevention and/or treatment of disorders involving aberrant protein expression or biological activity.



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The present invention further relates to methods for detecting the presence of the polynucleotides or polypeptides of the invention in a sample. Such methods can, for example, be utilized as part of prognostic and diagnostic evaluation of disorders as recited herein and for the identification of subjects exhibiting a predisposition to such conditions. The invention provides a method for detecting the polynucleotides of the invention in a sample, comprising contacting the sample with a compound that binds to and forms a complex with the polynucleotide of interest for a period sufficient to form the complex and under conditions sufficient to form a complex and detecting the complex such that if a complex is detected, the polynucleotide of interest is detected. The invention also provides a method for detecting the polypeptides of the invention in a sample comprising contacting the sample with a compound that binds to and forms a complex with the polypeptide under conditions and for a period sufficient to form the complex and detecting the formation of the complex such that if a complex is formed, the polypeptide is detected.

The invention also provides kits comprising polynucleotide probes and/or monoclonal antibodies, and optionally quantitative standards, for carrying out methods of the invention. Furthermore, the invention provides methods for evaluating the efficacy of drugs, and monitoring the progress of patients, involved in clinical trials for the treatment of disorders as recited above.

The invention also provides methods for the identification of compounds that modulate (i.e., increase or decrease) the expression or activity of the polynucleotides and/or polypeptides of the invention. Such methods can be utilized, for example, for the identification of compounds that can ameliorate symptoms of disorders as recited herein. Such methods can include, but are not limited to, assays for identifying compounds and other substances that interact with (e.g., bind to) the polypeptides of the invention. The invention provides a method for identifying a compound that binds to the polypeptides of the invention comprising contacting the compound with a polypeptide of the invention in a cell for a time sufficient to form a polypeptide/compound complex, wherein the complex drives expression of a reporter gene sequence expression such that if expression of the reporter gene is detected the compound the binds to a polypeptide of the invention is identified.

The methods of the invention also provides methods for treatment which involve the administration of the polynucleotides or polypeptides of the invention to individuals exhibiting symptoms or tendencies. In addition, the invention encompasses methods for treating diseases or disorders as recited herein comprising administering compounds and other substances that modulate the overall activity of the target gene products. Compounds and other substances can

effect such modulation either on the level of target gene/protein expression or target protein activity.

The polypeptides of the present invention and the polynucleotides encoding them are also useful for the same functions known to one of skill in the art as the polypeptides and polynucleotides to which they have homology (set forth in Table 2); for which they have a signature region (as set forth in Table 3); or for which they have homology to a gene family (as set forth in Table 4). If no homology is set forth for a sequence, then the polypeptides and polynucleotides of the present invention are useful for a variety of applications, as described herein, including use in arrays for detection.

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#### 4. DETAILED DESCRIPTION OF THE INVENTION

#### 4.1 DEFINITIONS.

It must be noted that as used herein and in the appended claims, the singular forms "a", "an" and "the" include plural references unless the context clearly dictates otherwise.

The term "active" refers to those forms of the polypeptide which retain the biologic and/or immunologic activities of any naturally occurring polypeptide. According to the invention, the terms "biologically active" or "biological activity" refer to a protein or peptide having structural, regulatory or biochemical functions of a naturally occurring molecule. Likewise "immunologically active" or "immunological activity" refers to the capability of the natural, recombinant or synthetic polypeptide to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

The term "activated cells" as used in this application are those cells which are engaged in extracellular or intracellular membrane trafficking, including the export of secretory or enzymatic molecules as part of a normal or disease process.

The terms "complementary" or "complementarity" refer to the natural binding of polynucleotides by base pairing. For example, the sequence 5'-AGT-3' binds to the complementary sequence 3'-TCA-5'. Complementarity between two single-stranded molecules may be "partial" such that only some of the nucleic acids bind or it may be "complete" such that total complementarity exists between the single stranded molecules. The degree of complementarity between the nucleic acid strands has significant effects on the efficiency and strength of the hybridization between the nucleic acid strands.

The term "embryonic stem cells (ES)" refers to a cell that can give rise to many differentiated cell types in an embryo or an adult, including the germ cells. The term "germ line stem cells (GSCs)" refers to stem cells derived from primordial stem cells that provide a steady

and continuous source of germ cells for the production of gametes. The term "primordial germ cells (PGCs)" refers to a small population of cells set aside from other cell lineages particularly from the yolk sac, mesenteries, or gonadal ridges during embryogenesis that have the potential to differentiate into germ cells and other cells. PGCs are the source from which GSCs and ES cells are derived The PGCs, the GSCs and the ES cells are capable of self-renewal. Thus these cells not only populate the germ line and give rise to a plurality of terminally differentiated cells that comprise the adult specialized organs, but are able to regenerate themselves.

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The term "expression modulating fragment," EMF, means a series of nucleotides which modulates the expression of an operably linked ORF or another EMF.

As used herein, a sequence is said to "modulate the expression of an operably linked sequence" when the expression of the sequence is altered by the presence of the EMF. EMFs include, but are not limited to, promoters, and promoter modulating sequences (inducible elements). One class of EMFs are nucleic acid fragments which induce the expression of an operably linked ORF in response to a specific regulatory factor or physiological event.

The terms "nucleotide sequence" or "nucleic acid" or "polynucleotide" or "oligonculeotide" are used interchangeably and refer to a heteropolymer of nucleotides or the sequence of these nucleotides. These phrases also refer to DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA) or to any DNA-like or RNA-like material. In the sequences herein A is adenine, C is cytosine, T is thymine, G is guanine and N is A, C, G or T (U). It is contemplated that where the polynucleotide is RNA, the T (thymine) in the sequences provided herein is substituted with U (uracil). Generally, nucleic acid segments provided by this invention may be assembled from fragments of the genome and short oligonucleotide linkers, or from a series of oligonucleotides, or from individual nucleotides, to provide a synthetic nucleic acid which is capable of being expressed in a recombinant transcriptional unit comprising regulatory elements derived from a microbial or viral operon, or a eukaryotic gene.

The terms "oligonucleotide fragment" or a "polynucleotide fragment", "portion," or "segment" or "probe" or "primer" are used interchangeably and refer to a sequence of nucleotide residues which are at least about 5 nucleotides, more preferably at least about 7 nucleotides, more preferably at least about 11 nucleotides and most preferably at least about 17 nucleotides. The fragment is preferably less than about 500 nucleotides, preferably less than about 200 nucleotides, more preferably less than about 100 nucleotides, more preferably less than about 50 nucleotides and most preferably less than 30 nucleotides. Preferably the probe is from about 6 nucleotides to about 200 nucleotides, preferably from about 15 to about 50 nucleotides, more preferably from about 17 to 30

nucleotides and most preferably from about 20 to 25 nucleotides. Preferably the fragments can be used in polymerase chain reaction (PCR), various hybridization procedures or microarray procedures to identify or amplify identical or related parts of mRNA or DNA molecules. A fragment or segment may uniquely identify each polynucleotide sequence of the present invention. Preferably the fragment comprises a sequence substantially similar to any one of SEQ ID NOs:1-20.

Probes may, for example, be used to determine whether specific mRNA molecules are present in a cell or tissue or to isolate similar nucleic acid sequences from chromosomal DNA as described by Walsh et al. (Walsh, P.S. et al., 1992, PCR Methods Appl 1:241-250). They may be labeled by nick translation, Klenow fill-in reaction, PCR, or other methods well known in the art. Probes of the present invention, their preparation and/or labeling are elaborated in Sambrook, J. et al., 1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, NY; or Ausubel, F.M. et al., 1989, Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, both of which are incorporated herein by reference in their entirety.

The nucleic acid sequences of the present invention also include the sequence information from the nucleic acid sequences of SEQ ID NO:1-236 and 473-708. The sequence information can be a segment of any one of SEQ ID NO:1-236 and 473-708 that uniquely identifies or represents the sequence information of that sequence of SEQ ID NO:1-236 and 473-708. One such segment can be a twenty-mer nucleic acid sequence because the probability that a twenty-mer is fully matched in the human genome is 1 in 300. In the human genome, there are three billion base pairs in one set of chromosomes. Because 4<sup>20</sup> possible twenty-mers exist, there are 300 times more twenty-mers than there are base pairs in a set of human chromosomes. Using the same analysis, the probability for a seventeen-mer to be fully matched in the human genome is approximately 1 in 5. When these segments are used in arrays for expression studies, fifteen-mer segments can be used. The probability that the fifteen-mer is fully matched in the expressed sequences is also approximately one in five because expressed sequences comprise less than approximately 5% of the entire genome sequence.

Similarly, when using sequence information for detecting a single mismatch, a segment can be a twenty-five mer. The probability that the twenty-five mer would appear in a human genome with a single mismatch is calculated by multiplying the probability for a full match  $(1 \div 4^{25})$  times the increased probability for mismatch at each nucleotide position  $(3 \times 25)$ . The probability that an eighteen mer with a single mismatch can be detected in an array for expression studies is approximately one in five. The probability that a twenty-mer with a single mismatch can be detected in a human genome is approximately one in five.

The term "open reading frame," ORF, means a series of nucleotide triplets coding for amino acids without any termination codons and is a sequence translatable into protein.

The terms "operably linked" or "operably associated" refer to functionally related nucleic acid sequences. For example, a promoter is operably associated or operably linked with a coding sequence if the promoter controls the transcription of the coding sequence. While operably linked nucleic acid sequences can be contiguous and in the same reading frame, certain genetic elements e.g. repressor genes are not contiguously linked to the coding sequence but still control transcription/translation of the coding sequence.

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The term "pluripotent" refers to the capability of a cell to differentiate into a number of differentiated cell types that are present in an adult organism. A pluripotent cell is restricted in its differentiation capability in comparison to a totipotent cell.

The terms "polypeptide" or "peptide" or "amino acid sequence" refer to an oligopeptide, peptide, polypeptide or protein sequence or fragment thereof and to naturally occurring or synthetic molecules. A polypeptide "fragment," "portion," or "segment" is a stretch of amino acid residues of at least about 5 amino acids, preferably at least about 7 amino acids, more preferably at least about 9 amino acids and most preferably at least about 17 or more amino acids. The peptide preferably is not greater than about 500 amino acids, more preferably less than 200 amino acids more preferably less than 150 amino acids and most preferably less than 100 amino acids. Preferably the peptide is from about 5 to about 200 amino acids. To be active, any polypeptide must have sufficient length to display biological and/or immunological activity.

The term "naturally occurring polypeptide" refers to polypeptides produced by cells that have not been genetically engineered and specifically contemplates various polypeptides arising from post-translational modifications of the polypeptide including, but not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation and acylation.

The term "translated protein coding portion" means a sequence which encodes for the full

The term "derivative" refers to polypeptides chemically modified by such techniques as ubiquitination, labeling (e.g., with radionuclides or various enzymes), covalent polymer attachment such as pegylation (derivatization with polyethylene glycol) and insertion or substitution by chemical synthesis of amino acids such as ornithine, which do not normally occur in human proteins.

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The term "variant" (or "analog") refers to any polypeptide differing from naturally occurring polypeptides by amino acid insertions, deletions, and substitutions, created using, e g., recombinant DNA techniques. Guidance in determining which amino acid residues may be replaced, added or deleted without abolishing activities of interest, may be found by comparing the sequence of the particular polypeptide with that of homologous peptides and minimizing the number of amino acid sequence changes made in regions of high homology (conserved regions) or by replacing amino acids with consensus sequence.

Alternatively, recombinant variants encoding these same or similar polypeptides may be synthesized or selected by making use of the "redundancy" in the genetic code. Various codon substitutions, such as the silent changes which produce various restriction sites, may be introduced to optimize cloning into a plasmid or viral vector or expression in a particular prokaryotic or eukaryotic system. Mutations in the polynucleotide sequence may be reflected in the polypeptide or domains of other peptides added to the polypeptide to modify the properties of any part of the polypeptide, to change characteristics such as ligand-binding affinities, interchain affinities, or degradation/turnover rate.

Preferably, amino acid "substitutions" are the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, *i.e.*, conservative amino acid replacements. "Conservative" amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophobicity, and/or the amphipathic nature of the residues involved. For example, nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, and methionine; polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine; positively charged (basic) amino acids include arginine, lysine, and histidine; and negatively charged (acidic) amino acids include aspartic acid and glutamic acid. "Insertions" or "deletions" are preferably in the range of about 1 to 20 amino acids, more preferably 1 to 10 amino acids. The variation allowed may be experimentally determined by systematically making insertions, deletions, or substitutions of amino acids in a polypeptide molecule using recombinant DNA techniques and assaying the resulting recombinant variants for activity.

Alternatively, where alteration of function is desired, insertions, deletions or non-conservative alterations can be engineered to produce altered polypeptides. Such alterations

can, for example, alter one or more of the biological functions or biochemical characteristics of the polypeptides of the invention. For example, such alterations may change polypeptide characteristics such as ligand-binding affinities, interchain affinities, or degradation/turnover rate. Further, such alterations can be selected so as to generate polypeptides that are better suited for expression, scale up and the like in the host cells chosen for expression. For example, cysteine residues can be deleted or substituted with another amino acid residue in order to eliminate disulfide bridges.

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The terms "purified" or "substantially purified" as used herein denotes that the indicated nucleic acid or polypeptide is present in the substantial absence of other biological macromolecules, e.g., polynucleotides, proteins, and the like. In one embodiment, the polynucleotide or polypeptide is purified such that it constitutes at least 95% by weight, more preferably at least 99% by weight, of the indicated biological macromolecules present (but water, buffers, and other small molecules, especially molecules having a molecular weight of less than 1000 daltons, can be present).

The term "isolated" as used herein refers to a nucleic acid or polypeptide separated from at least one other component (e.g., nucleic acid or polypeptide) present with the nucleic acid or polypeptide in its natural source. In one embodiment, the nucleic acid or polypeptide is found in the presence of (if anything) only a solvent, buffer, ion, or other component normally present in a solution of the same. The terms "isolated" and "purified" do not encompass nucleic acids or polypeptides present in their natural source.

The term "recombinant," when used herein to refer to a polypeptide or protein, means that a polypeptide or protein is derived from recombinant (e.g., microbial, insect, or mammalian) expression systems. "Microbial" refers to recombinant polypeptides or proteins made in bacterial or fungal (e.g., yeast) expression systems. As a product, "recombinant microbial" defines a polypeptide or protein essentially free of native endogenous substances and unaccompanied by associated native glycosylation. Polypeptides or proteins expressed in most bacterial cultures, e.g., E. coli, will be free of glycosylation modifications; polypeptides or proteins expressed in yeast will have a glycosylation pattern in general different from those expressed in mammalian cells.

The term "recombinant expression vehicle or vector" refers to a plasmid or phage or virus or vector, for expressing a polypeptide from a DNA (RNA) sequence. An expression vehicle can comprise a transcriptional unit comprising an assembly of (1) a genetic element or elements having a regulatory role in gene expression, for example, promoters or enhancers, (2) a structural or coding sequence which is transcribed into mRNA and translated into protein, and (3) appropriate transcription initiation and termination sequences. Structural units intended for use

in yeast or eukaryotic expression systems preferably include a leader sequence enabling extracellular secretion of translated protein by a host cell. Alternatively, where recombinant protein is expressed without a leader or transport sequence, it may include an amino terminal methionine residue. This residue may or may not be subsequently cleaved from the expressed recombinant protein to provide a final product.

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The term "recombinant expression system" means host cells which have stably integrated a recombinant transcriptional unit into chromosomal DNA or carry the recombinant transcriptional unit extrachromosomally. Recombinant expression systems as defined herein will express heterologous polypeptides or proteins upon induction of the regulatory elements linked to the DNA segment or synthetic gene to be expressed. This term also means host cells which have stably integrated a recombinant genetic element or elements having a regulatory role in gene expression, for example, promoters or enhancers. Recombinant expression systems as defined herein will express polypeptides or proteins endogenous to the cell upon induction of the regulatory elements linked to the endogenous DNA segment or gene to be expressed. The cells can be prokaryotic or eukaryotic.

The term "secreted" includes a protein that is transported across or through a membrane, including transport as a result of signal sequences in its amino acid sequence when it is expressed in a suitable host cell. "Secreted" proteins include without limitation proteins secreted wholly (e.g., soluble proteins) or partially (e.g., receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins that are transported across the membrane of the endoplasmic reticulum. "Secreted" proteins are also intended to include proteins containing non-typical signal sequences (e.g. Interleukin-1 Beta, see Krasney, P.A. and Young, P.R. (1992) Cytokine 4(2):134 -143) and factors released from damaged cells (e.g. Interleukin-1 Receptor Antagonist, see Arend, W.P. et. al. (1998) Annu. Rev. Immunol. 16:27-55)

Where desired, an expression vector may be designed to contain a "signal or leader sequence" which will direct the polypeptide through the membrane of a cell. Such a sequence may be naturally present on the polypeptides of the present invention or provided from heterologous protein sources by recombinant DNA techniques.

The term "stringent" is used to refer to conditions that are commonly understood in the art as stringent. Stringent conditions can include highly stringent conditions (i.e., hybridization to filter-bound DNA in 0.5 M NaHPO<sub>4</sub>, 7% sodium dodecyl sulfate (SDS), 1 mM EDTA at 65°C, and washing in 0.1X SSC/0.1% SDS at 68°C), and moderately stringent conditions (i.e., washing in 0.2X SSC/0.1% SDS at 42°C). Other exemplary hybridization conditions are described herein in the examples.

In instances of hybridization of deoxyoligonucleotides, additional exemplary stringent hybridization conditions include washing in 6X SSC/0.05% sodium pyrophosphate at 37°C (for 14-base oligonucleotides), 48°C (for 17-base oligos), 55°C (for 20-base oligonucleotides), and 60°C (for 23-base oligonucleotides).

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As used herein, "substantially equivalent" can refer both to nucleotide and amino acid sequences, for example a mutant sequence, that varies from a reference sequence by one or more substitutions, deletions, or additions, the net effect of which does not result in an adverse functional dissimilarity between the reference and subject sequences. Typically, such a substantially equivalent sequence varies from one of those listed herein by no more than about 35% (i.e., the number of individual residue substitutions, additions, and/or deletions in a substantially equivalent sequence, as compared to the corresponding reference sequence, divided by the total number of residues in the substantially equivalent sequence is about 0.35 or less). Such a sequence is said to have 65% sequence identity to the listed sequence. In one embodiment, a substantially equivalent, e.g., mutant, sequence of the invention varies from a listed sequence by no more than 30% (70% sequence identity); in a variation of this embodiment, by no more than 25% (75% sequence identity); and in a further variation of this embodiment, by no more than 20% (80% sequence identity) and in a further variation of this embodiment, by no more than 10% (90% sequence identity) and in a further variation of this embodiment, by no more that 5% (95% sequence identity). Substantially equivalent, e.g., mutant, amino acid sequences according to the invention preferably have at least 80% sequence identity with a listed amino acid sequence, more preferably at least 90% sequence identity. Substantially equivalent nucleotide sequences of the invention can have lower percent sequence identities, taking into account, for example, the redundancy or degeneracy of the genetic code. Preferably, nucleotide sequence has at least about 65% identity, more preferably at least about 75% identity, and most preferably at least about 95% identity. For the purposes of the present invention, sequences having substantially equivalent biological activity and substantially equivalent expression characteristics are considered substantially equivalent. For the purposes of determining equivalence, truncation of the mature sequence (e.g., via a mutation which creates a spurious stop codon) should be disregarded. Sequence identity may be determined, e.g., using the Jotun Hein method (Hein, J. (1990) Methods Enzymol. 183:626-645). Identity between sequences can also be determined by other methods known in the art, e.g. by varying hybridization conditions.

The term "totipotent" refers to the capability of a cell to differentiate into all of the cell types of an adult organism.

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The term "transformation" means introducing DNA into a suitable host cell so that the DNA is replicable, either as an extrachromosomal element, or by chromosomal integration. The term "transfection" refers to the taking up of an expression vector by a suitable host cell, whether or not any coding sequences are in fact expressed. The term "infection" refers to the introduction of nucleic acids into a suitable host cell by use of a virus or viral vector.

As used herein, an "uptake modulating fragment," UMF, means a series of nucleotides which mediate the uptake of a linked DNA fragment into a cell. UMFs can be readily identified using known UMFs as a target sequence or target motif with the computer-based systems described below. The presence and activity of a UMF can be confirmed by attaching the suspected UMF to a marker sequence. The resulting nucleic acid molecule is then incubated with an appropriate host under appropriate conditions and the uptake of the marker sequence is determined. As described above, a UMF will increase the frequency of uptake of a linked marker sequence.

Each of the above terms is meant to encompass all that is described for each, unless the context dictates otherwise.

# 4.2 NUCLEIC ACIDS OF THE INVENTION

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Nucleotide sequences of the invention are set forth in the Sequence Listing.

The isolated polynucleotides of the invention include a polynucleotide comprising the nucleotide sequences of SEQ ID NO:1-236 and 473-708; a polynucleotide encoding any one of the peptide sequences of SEQ ID NO:237-472 and 709-944; and a polynucleotide comprising the nucleotide sequence encoding the mature protein coding sequence of the polypeptides of any one of SEQ ID NO:237-472 and 709-944. The polynucleotides of the present invention also include, but are not limited to, a polynucleotide that hybridizes under stringent conditions to (a) the complement of any of the nucleotides sequences of SEQ ID NO:1-236 and 473-708; (b) nucleotide sequences encoding any one of the amino acid sequences set forth in the Sequence Listing as SEQ ID NO:237-472 and 709-944; (c) a polynucleotide which is an allelic variant of any polynucleotide recited above; (d) a polynucleotide which encodes a species homolog of any of the proteins recited above; or (e) a polynucleotide that encodes a polypeptide comprising a specific domain or truncation of the polypeptides of SEQ ID NO:237-472 and 709-944. Domains of interest may depend on the nature of the encoded polypeptide; e.g., domains in receptor-like polypeptides include ligand-binding, extracellular, transmembrane, or cytoplasmic domains, or combinations thereof; domains in immunoglobulin-like proteins include the variable immunoglobulin-like domains; domains in enzyme-like polypeptides include catalytic and

substrate binding domains; and domains in ligand polypeptides include receptor-binding domains.

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The polynucleotides of the invention include naturally occurring or wholly or partially synthetic DNA, e.g., cDNA and genomic DNA, and RNA, e.g., mRNA. The polynucleotides may include all of the coding region of the cDNA or may represent a portion of the coding region of the cDNA.

The present invention also provides genes corresponding to the cDNA sequences disclosed herein. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. Further 5' and 3' sequence can be obtained using methods known in the art. For example, full length cDNA or genomic DNA that corresponds to any of the polynucleotides of SEQ ID NO:1-236 and 473-708 can be obtained by screening appropriate cDNA or genomic DNA libraries under suitable hybridization conditions using any of the polynucleotides of SEQ ID NO:1-236 and 473-708 or a portion thereof as a probe. Alternatively, the polynucleotides of SEQ ID NO:1-236 and 473-708 may be used as the basis for suitable primer(s) that allow identification and/or amplification of genes in appropriate genomic DNA or cDNA libraries.

The nucleic acid sequences of the invention can be assembled from ESTs and sequences (including cDNA and genomic sequences) obtained from one or more public databases, such as dbEST, gbpri, and UniGene. The EST sequences can provide identifying sequence information, representative fragment or segment information, or novel segment information for the full-length gene.

The polynucleotides of the invention also provide polynucleotides including nucleotide sequences that are substantially equivalent to the polynucleotides recited above. Polynucleotides according to the invention can have, e.g., at least about 65%, at least about 70%, at least about 75%, at least about 80%, more typically at least about 90%, and even more typically at least about 95%, sequence identity to a polynucleotide recited above.

Included within the scope of the nucleic acid sequences of the invention are nucleic acid sequence fragments that hybridize under stringent conditions to any of the nucleotide sequences of SEQ ID NO:1-236 and 473-708, or complements thereof, which fragment is greater than about 5 nucleotides, preferably 7 nucleotides, more preferably greater than 9 nucleotides and most preferably greater than 17 nucleotides. Fragments of, e.g. 15, 17, or 20 nucleotides or more that are selective for (i.e. specifically hybridize to any one of the polynucleotides of the invention) are contemplated. Probes capable of specifically hybridizing to a polynucleotide can

differentiate polynucleotide sequences of the invention from other polynucleotide sequences in the same family of genes or can differentiate human genes from genes of other species, and are preferably based on unique nucleotide sequences.

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The sequences falling within the scope of the present invention are not limited to these specific sequences, but also include allelic and species variations thereof. Allelic and species variations can be routinely determined by comparing the sequence provided SEQ ID NO:1-236 and 473-708, a representative fragment thereof, or a nucleotide sequence at least 90% identical, preferably 95% identical, to SEQ ID NO:1-236 and 473-708 with a sequence from another isolate of the same species. Furthermore, to accommodate codon variability, the invention includes nucleic acid molecules coding for the same amino acid sequences as do the specific ORFs disclosed herein. In other words, in the coding region of an ORF, substitution of one codon for another codon that encodes the same amino acid is expressly contemplated.

The nearest neighbor or homology result for the nucleic acids of the present invention, including SEQ ID NO:1-236 and 473-708, can be obtained by searching a database using an algorithm or a program. Preferably, a BLAST which stands for Basic Local Alignment Search Tool is used to search for local sequence alignments (Altshul, S.F. J Mol. Evol. 36 290-300 (1993) and Altschul S.F. et al. J. Mol. Biol. 21:403-410 (1990)). Alternatively a FASTA version 3 search against Genpept, using Fastxy algorithm.

Species homologs (or orthologs) of the disclosed polynucleotides and proteins are also provided by the present invention. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous or related to that encoded by the polynucleotides.

The nucleic acid sequences of the invention are further directed to sequences which encode variants of the described nucleic acids. These amino acid sequence variants may be prepared by methods known in the art by introducing appropriate nucleotide changes into a native or variant polynucleotide. There are two variables in the construction of amino acid sequence variants: the location of the mutation and the nature of the mutation. Nucleic acids encoding the amino acid sequence variants are preferably constructed by mutating the polynucleotide to encode an amino acid sequence that does not occur in nature. These nucleic acid alterations can be made at sites that differ in the nucleic acids from different species (variable positions) or in highly conserved regions (constant regions). Sites at such locations

will typically be modified in series, e.g., by substituting first with conservative choices (e.g., hydrophobic amino acid to a different hydrophobic amino acid) and then with more distant choices (e.g., hydrophobic amino acid to a charged amino acid), and then deletions or insertions may be made at the target site. Amino acid sequence deletions generally range from about 1 to 30 residues, preferably about 1 to 10 residues, and are typically contiguous. Amino acid insertions include amino- and/or carboxyl-terminal fusions ranging in length from one to one hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Intrasequence insertions may range generally from about 1 to 10 amino residues, preferably from 1 to 5 residues. Examples of terminal insertions include the heterologous signal sequences necessary for secretion or for intracellular targeting in different host cells and sequences such as FLAG or poly-histidine sequences useful for purifying the expressed protein.

In a preferred method, polynucleotides encoding the novel amino acid sequences are changed via site-directed mutagenesis. This method uses oligonucleotide sequences to alter a polynucleotide to encode the desired amino acid variant, as well as sufficient adjacent nucleotides on both sides of the changed amino acid to form a stable duplex on either side of the site of being changed. In general, the techniques of site-directed mutagenesis are well known to those of skill in the art and this technique is exemplified by publications such as, Edelman et al., DNA 2:183 (1983). A versatile and efficient method for producing site-specific changes in a polynucleotide sequence was published by Zoller and Smith, Nucleic Acids Res. 10:6487-6500 (1982). PCR may also be used to create amino acid sequence variants of the novel nucleic acids. When small amounts of template DNA are used as starting material, primer(s) that differs slightly in sequence from the corresponding region in the template DNA can generate the desired amino acid variant. PCR amplification results in a population of product DNA fragments that differ from the polynucleotide template encoding the polypeptide at the position specified by the primer. The product DNA fragments replace the corresponding region in the plasmid and this gives a polynucleotide encoding the desired amino acid variant.

A further technique for generating amino acid variants is the cassette mutagenesis technique described in Wells et al., *Gene* 34:315 (1985); and other mutagenesis techniques well known in the art, such as, for example, the techniques in Sambrook et al., supra, and *Current Protocols in Molecular Biology*, Ausubel et al. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be used in the practice of the invention for the cloning and expression of these novel nucleic acids. Such DNA sequences include those which are capable of hybridizing to the appropriate novel nucleic acid sequence under stringent conditions.

Polynucleotides encoding preferred polypeptide truncations of the invention can be used to generate polynucleotides encoding chimeric or fusion proteins comprising one or more domains of the invention and heterologous protein sequences.

The polynucleotides of the invention additionally include the complement of any of the polynucleotides recited above. The polynucleotide can be DNA (genomic, cDNA, amplified, or synthetic) or RNA. Methods and algorithms for obtaining such polynucleotides are well known to those of skill in the art and can include, for example, methods for determining hybridization conditions that can routinely isolate polynucleotides of the desired sequence identities.

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In accordance with the invention, polynucleotide sequences comprising the mature protein coding sequences corresponding to any one of SEQ ID NO:1-236 and 473-708, or functional equivalents thereof, may be used to generate recombinant DNA molecules that direct the expression of that nucleic acid, or a functional equivalent thereof, in appropriate host cells. Also included are the cDNA inserts of any of the clones identified herein.

A polynucleotide according to the invention can be joined to any of a variety of other nucleotide sequences by well-established recombinant DNA techniques (see Sambrook J et al. (1989) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, NY). Useful nucleotide sequences for joining to polynucleotides include an assortment of vectors, e.g., plasmids, cosmids, lambda phage derivatives, phagemids, and the like, that are well known in the art. Accordingly, the invention also provides a vector including a polynucleotide of the invention and a host cell containing the polynucleotide. In general, the vector contains an origin of replication functional in at least one organism, convenient restriction endonuclease sites, and a selectable marker for the host cell. Vectors according to the invention include expression vectors, replication vectors, probe generation vectors, and sequencing vectors. A host cell according to the invention can be a prokaryotic or eukaryotic cell and can be a unicellular organism or part of a multicellular organism.

The present invention further provides recombinant constructs comprising a nucleic acid having any of the nucleotide sequences of SEQ ID NO:1-236 and 473-708 or a fragment thereof or any other polynucleotides of the invention. In one embodiment, the recombinant constructs of the present invention comprise a vector, such as a plasmid or viral vector, into which a nucleic acid having any of the nucleotide sequences of SEQ ID NO:1-236 and 473-708 or a fragment thereof is inserted, in a forward or reverse orientation. In the case of a vector comprising one of the ORFs of the present invention, the vector may further comprise regulatory sequences, including for example, a promoter, operably linked to the ORF. Large numbers of suitable vectors and promoters are known to those of skill in the art and are commercially available for generating the recombinant constructs of the present invention. The following vectors are

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provided by way of example. Bacterial: pBs, phagescript, PsiX174, pBluescript SK, pBs KS, pNH8a, pNH16a, pNH18a, pNH46a (Stratagene); pTrc99A, pKK223-3, pKK233-3, pDR540, pRIT5 (Pharmacia). Eukaryotic: pWLneo, pSV2cat, pOG44, PXTI, pSG (Stratagene) pSVK3, pBPV, pMSG, pSVL (Pharmacia).

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The isolated polynucleotide of the invention may be operably linked to an expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman et al., Nucleic Acids Res. 19, 4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, Methods in Enzymology 185, 537-566 (1990). As defined herein "operably linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

Promoter regions can be selected from any desired gene using CAT (chloramphenicol transferase) vectors or other vectors with selectable markers. Two appropriate vectors are pKK232-8 and pCM7. Particular named bacterial promoters include lacI, lacZ, T3, T7, gpt, lambda PR, and trc. Eukaryotic promoters include CMV immediate early, HSV thymidine kinase, early and late SV40, LTRs from retrovirus, and mouse metallothionein-I. Selection of the appropriate vector and promoter is well within the level of ordinary skill in the art. Generally, recombinant expression vectors will include origins of replication and selectable markers permitting transformation of the host cell, e.g., the ampicillin resistance gene of E. coli and S. cerevisiae TRP1 gene, and a promoter derived from a highly-expressed gene to direct transcription of a downstream structural sequence. Such promoters can be derived from operons encoding glycolytic enzymes such as 3-phosphoglycerate kinase (PGK), a-factor, acid phosphatase, or heat shock proteins, among others. The heterologous structural sequence is assembled in appropriate phase with translation initiation and termination sequences, and preferably, a leader sequence capable of directing secretion of translated protein into the periplasmic space or extracellular medium. Optionally, the heterologous sequence can encode a fusion protein including an amino terminal identification peptide imparting desired characteristics, e.g., stabilization or simplified purification of expressed recombinant product. Useful expression vectors for bacterial use are constructed by inserting a structural DNA sequence encoding a desired protein together with suitable translation initiation and termination signals in operable reading phase with a functional promoter. The vector will comprise one or more phenotypic selectable markers and an origin of replication to ensure maintenance of the vector and to, if desirable, provide amplification within the host. Suitable prokaryotic hosts for

transformation include E. coli, Bacillus subtilis, Salmonella typhimurium and various species within the genera Pseudomonas, Streptomyces, and Staphylococcus, although others may also be employed as a matter of choice.

As a representative but non-limiting example, useful expression vectors for bacterial use can comprise a selectable marker and bacterial origin of replication derived from commercially available plasmids comprising genetic elements of the well known cloning vector pBR322 (ATCC 37017). Such commercial vectors include, for example, pKK223-3 (Pharmacia Fine Chemicals, Uppsala, Sweden) and GEM 1 (Promega Biotech, Madison, WI, USA). These pBR322 "backbone" sections are combined with an appropriate promoter and the structural sequence to be expressed. Following transformation of a suitable host strain and growth of the host strain to an appropriate cell density, the selected promoter is induced or derepressed by appropriate means (e.g., temperature shift or chemical induction) and cells are cultured for an additional period. Cells are typically harvested by centrifugation, disrupted by physical or chemical means, and the resulting crude extract retained for further purification.

Polynucleotides of the invention can also be used to induce immune responses. For example, as described in Fan et al., *Nat. Biotech.* 17:870-872 (1999), incorporated herein by reference, nucleic acid sequences encoding a polypeptide may be used to generate antibodies against the encoded polypeptide following topical administration of naked plasmid DNA or following injection, and preferably intramuscular injection of the DNA. The nucleic acid sequences are preferably inserted in a recombinant expression vector and may be in the form of naked DNA.

#### 4.3 ANTISENSE

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Another aspect of the invention pertains to isolated antisense nucleic acid molecules that are hybridizable to or complementary to the nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1-236 and 473-708, or fragments, analogs or derivatives thereof. An "antisense" nucleic acid comprises a nucleotide sequence that is complementary to a "sense" nucleic acid encoding a protein, *e.g.*, complementary to the coding strand of a double-stranded cDNA molecule or complementary to an mRNA sequence. In specific aspects, antisense nucleic acid molecules are provided that comprise a sequence complementary to at least about 10, 25, 50, 100, 250 or 500 nucleotides or an entire coding strand, or to only a portion thereof. Nucleic acid molecules encoding fragments, homologs, derivatives and analogs of a protein of any of SEQ ID NO:237-472 and 709-944 or antisense nucleic acids complementary to a nucleic acid sequence of SEQ ID NO:1-236 and 473-708 are additionally provided.

In one embodiment, an antisense nucleic acid molecule is antisense to a "coding region" of the coding strand of a nucleotide sequence of the invention. The term "coding region" refers to the region of the nucleotide sequence comprising codons which are translated into amino acid residues. In another embodiment, the antisense nucleic acid molecule is antisense to a "noncoding region" of the coding strand of a nucleotide sequence of the invention. The term "noncoding region" refers to 5' and 3' sequences which flank the coding region that are not translated into amino acids (i.e., also referred to as 5' and 3' untranslated regions).

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Given the coding strand sequences encoding a nucleic acid disclosed herein (e.g., SEQ ID NO:1-236 and 473-708), antisense nucleic acids of the invention can be designed according to the rules of Watson and Crick or Hoogsteen base pairing. The antisense nucleic acid molecule can be complementary to the entire coding region of a mRNA, but more preferably is an oligonucleotide that is antisense to only a portion of the coding or noncoding region of a mRNA. For example, the antisense oligonucleotide can be complementary to the region surrounding the translation start site of a mRNA. An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis or enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (e.g., an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, e.g., phosphorothioate derivatives and acridine substituted nucleotides can be used.

Examples of modified nucleotides that can be used to generate the antisense nucleic acid include: 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, 25 inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, 30 queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an antisense orientation (i.e., RNA transcribed from the 35

inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest, described further in the following subsection).

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The antisense nucleic acid molecules of the invention are typically administered to a subject or generated in situ such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding a protein according to the invention to thereby inhibit expression of the protein, e.g., by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule that binds to DNA duplexes, through specific interactions in the major groove of the double helix. An example of a route of administration of antisense nucleic acid molecules of the invention includes direct injection at a tissue site. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface, e.g., by linking the antisense nucleic acid molecules to peptides or antibodies that bind to cell surface receptors or antigens. The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of antisense molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

In yet another embodiment, the antisense nucleic acid molecule of the invention is an α-anomeric nucleic acid molecule. An α-anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β-units, the strands run parallel to each other (Gaultier *et al.* (1987) *Nucleic Acids Res* 15: 6625-6641). The antisense nucleic acid molecule can also comprise a 2'-o-methylribonucleotide (Inoue *et al.* (1987) *Nucleic Acids Res* 15: 6131-6148) or a chimeric RNA -DNA analogue (Inoue *et al.* (1987) *FEBS Lett* 215: 327-330).

### 4.4 RIBOZYMES AND PNA MOIETIES

In still another embodiment, an antisense nucleic acid of the invention is a ribozyme. Ribozymes are catalytic RNA molecules with ribonuclease activity that are capable of cleaving a single-stranded nucleic acid, such as a mRNA, to which they have a complementary region. Thus, ribozymes (e.g., hammerhead ribozymes (described in Haselhoff and Gerlach (1988) Nature 334:585-591)) can be used to catalytically cleave a mRNA transcripts to thereby inhibit translation of a mRNA. A ribozyme having specificity for a nucleic acid of the invention can be designed based upon the nucleotide sequence of a DNA disclosed herein (i.e., SEQ ID NO:1-236 and 473-708). For example, a derivative of a Tetrahymena L-19 IVS RNA can be constructed in

which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in a SECX-encoding mRNA. See, e.g., Cech et al. U.S. Pat. No. 4,987,071; and Cech et al. U.S. Pat. No. 5,116,742. Alternatively, SECX mRNA can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules. See, e.g., Bartel et al., (1993) Science 261:1411-1418.

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Alternatively, gene expression can be inhibited by targeting nucleotide sequences complementary to the regulatory region (e.g., promoter and/or enhancers) to form triple helical structures that prevent transcription of the gene in target cells. See generally, Helene. (1991) Anticancer Drug Des. 6: 569-84; Helene. et al. (1992) Ann. N.Y. Acad. Sci. 660:27-36; and Maher (1992) Bioassays 14: 807-15.

In various embodiments, the nucleic acids of the invention can be modified at the base moiety, sugar moiety or phosphate backbone to improve, e.g., the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acids can be modified to generate peptide nucleic acids (see Hyrup et al. (1996) Bioorg Med Chem 4: 5-23). As used herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics, e.g., DNA mimics, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described in Hyrup et al. (1996) above; Perry-O'Keefe et al. (1996) PNAS 93: 14670-675.

PNAs of the invention can be used in therapeutic and diagnostic applications. For example, PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, e.g., inducing transcription or translation arrest or inhibiting replication. PNAs of the invention can also be used, e.g., in the analysis of single base pair mutations in a gene by, e.g., PNA directed PCR clamping; as artificial restriction enzymes when used in combination with other enzymes, e.g., S1 nucleases (Hyrup B. (1996) above); or as probes or primers for DNA sequence and hybridization (Hyrup et al. (1996), above; Perry-O'Keefe (1996), above).

In another embodiment, PNAs of the invention can be modified, e.g., to enhance their stability or cellular uptake, by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras can be generated that may combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes, e.g., RNase H and DNA polymerases, to interact with the DNA portion while the PNA

portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation (Hyrup (1996) above). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup (1996) above and Finn et al. (1996) Nucl Acids Res 24: 3357-63. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry, and modified nucleoside analogs, e.g., 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine phosphoramidite, can be used between the PNA and the 5' end of DNA (Mag et al. (1989) Nucl Acid Res 17: 5973-88). PNA monomers are then coupled in a stepwise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment (Finn et al. (1996) above). Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment. See, Petersen et al. (1975) Bioorg Med Chem Lett 5: 1119-11124.

In other embodiments, the oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptors in vivo), or agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., 1989, Proc. Natl. Acad. Sci. U.S.A. 86:6553-6556; Lemaitre et al., 1987, Proc. Natl. Acad. Sci. 84:648-652; PCT Publication No. W088/09810) or the blood-brain barrier (see, e.g., PCT Publication No. W089/10134). In addition, oligonucleotides can be modified with hybridization triggered cleavage agents (See, e.g., Krol et al., 1988, BioTechniques 6:958-976) or intercalating agents. (See, e.g., Zon, 1988, Pharm. Res. 5: 539-549). To this end, the oligonucleotide may be conjugated to another molecule, e.g., a peptide, a hybridization triggered cross-linking agent, a transport agent, a hybridization-triggered cleavage agent, etc.

#### 4.5 HOSTS

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The present invention further provides host cells genetically engineered to contain the polynucleotides of the invention. For example, such host cells may contain nucleic acids of the invention introduced into the host cell using known transformation, transfection or infection methods. The present invention still further provides host cells genetically engineered to express the polynucleotides of the invention, wherein such polynucleotides are in operative association with a regulatory sequence heterologous to the host cell which drives expression of the polynucleotides in the cell.

Knowledge of nucleic acid sequences allows for modification of cells to permit, or increase, expression of endogenous polypeptide. Cells can be modified (e.g., by homologous recombination) to provide increased polypeptide expression by replacing, in whole or in part, the naturally occurring promoter with all or part of a heterologous promoter so that the cells express

the polypeptide at higher levels. The heterologous promoter is inserted in such a manner that it is operatively linked to the encoding sequences. See, for example, PCT International Publication No. WO94/12650, PCT International Publication No. WO92/20808, and PCT International Publication No. WO91/09955. It is also contemplated that, in addition to heterologous promoter DNA, amplifiable marker DNA (e.g., ada, dhfr, and the multifunctional CAD gene which encodes carbamyl phosphate synthase, aspartate transcarbamylase, and dihydroorotase) and/or intron DNA may be inserted along with the heterologous promoter DNA. If linked to the coding sequence, amplification of the marker DNA by standard selection methods results in coamplification of the desired protein coding sequences in the cells.

The host cell can be a higher eukaryotic host cell, such as a mammalian cell, a lower eukaryotic host cell, such as a yeast cell, or the host cell can be a prokaryotic cell, such as a bacterial cell. Introduction of the recombinant construct into the host cell can be effected by calcium phosphate transfection, DEAE, dextran mediated transfection, or electroporation (Davis, L. et al., *Basic Methods in Molecular Biology* (1986)). The host cells containing one of the polynucleotides of the invention, can be used in conventional manners to produce the gene product encoded by the isolated fragment (in the case of an ORF) or can be used to produce a heterologous protein under the control of the EMF.

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Any host/vector system can be used to express one or more of the ORFs of the present invention. These include, but are not limited to, eukaryotic hosts such as HeLa cells, Cv-1 cell, COS cells, 293 cells, and Sf9 cells, as well as prokaryotic host such as *E. coli* and *B. subtilis*. The most preferred cells are those which do not normally express the particular polypeptide or protein or which expresses the polypeptide or protein at low natural level. Mature proteins can be expressed in mammalian cells, yeast, bacteria, or other cells under the control of appropriate promoters. Cell-free translation systems can also be employed to produce such proteins using RNAs derived from the DNA constructs of the present invention. Appropriate cloning and expression vectors for use with prokaryotic and eukaryotic hosts are described by Sambrook, et al., in Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor, New York (1989), the disclosure of which is hereby incorporated by reference.

Various mammalian cell culture systems can also be employed to express recombinant protein. Examples of mammalian expression systems include the COS-7 lines of monkey kidney fibroblasts, described by Gluzman, Cell 23:175 (1981). Other cell lines capable of expressing a compatible vector are, for example, the C127, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from *in vitro* culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK,

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HL-60, U937, HaK or Jurkat cells. Mammalian expression vectors will comprise an origin of replication, a suitable promoter and also any necessary ribosome binding sites, polyadenylation site, splice donor and acceptor sites, transcriptional termination sequences, and 5' flanking nontranscribed sequences. DNA sequences derived from the SV40 viral genome, for example, SV40 origin, early promoter, enhancer, splice, and polyadenylation sites may be used to provide the required nontranscribed genetic elements. Recombinant polypeptides and proteins produced in bacterial culture are usually isolated by initial extraction from cell pellets, followed by one or more salting-out, aqueous ion exchange or size exclusion chromatography steps. Protein refolding steps can be used, as necessary, in completing configuration of the mature protein. Finally, high performance liquid chromatography (HPLC) can be employed for final purification steps. Microbial cells employed in expression of proteins can be disrupted by any convenient method, including freeze-thaw cycling, sonication, mechanical disruption, or use of cell lysing agents.

Alternatively, it may be possible to produce the protein in lower eukaryotes such as yeast or insects or in prokaryotes such as bacteria. Potentially suitable yeast strains include Saccharomyces cerevisiae, Schizosaccharomyces pombe, Kluyveromyces strains, Candida, or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include Escherichia coli, Bacillus subtilis, Salmonella typhimurium, or any bacterial strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional protein. Such covalent attachments may be accomplished using known chemical or enzymatic methods.

In another embodiment of the present invention, cells and tissues may be engineered to express an endogenous gene comprising the polynucleotides of the invention under the control of inducible regulatory elements, in which case the regulatory sequences of the endogenous gene may be replaced by homologous recombination. As described herein, gene targeting can be used to replace a gene's existing regulatory region with a regulatory sequence isolated from a different gene or a novel regulatory sequence synthesized by genetic engineering methods. Such regulatory sequences may be comprised of promoters, enhancers, scaffold-attachment regions, negative regulatory elements, transcriptional initiation sites, regulatory protein binding sites or combinations of said sequences. Alternatively, sequences which affect the structure or stability of the RNA or protein produced may be replaced, removed, added, or otherwise modified by targeting. These sequence include polyadenylation signals, mRNA stability elements, splice sites, leader sequences for enhancing or modifying transport or secretion properties of the

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protein, or other sequences which alter or improve the function or stability of protein or RNA molecules.

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The targeting event may be a simple insertion of the regulatory sequence, placing the gene under the control of the new regulatory sequence, e.g., inserting a new promoter or enhancer or both upstream of a gene. Alternatively, the targeting event may be a simple deletion of a regulatory element, such as the deletion of a tissue-specific negative regulatory element. Alternatively, the targeting event may replace an existing element; for example, a tissue-specific enhancer can be replaced by an enhancer that has broader or different cell-type specificity than the naturally occurring elements. Here, the naturally occurring sequences are deleted and new sequences are added. In all cases, the identification of the targeting event may be facilitated by the use of one or more selectable marker genes that are contiguous with the targeting DNA, allowing for the selection of cells in which the exogenous DNA has integrated into the host cell genome. The identification of the targeting event may also be facilitated by the use of one or more marker genes exhibiting the property of negative selection, such that the negatively selectable marker is linked to the exogenous DNA, but configured such that the negatively selectable marker flanks the targeting sequence, and such that a correct homologous recombination event with sequences in the host cell genome does not result in the stable integration of the negatively selectable marker. Markers useful for this purpose include the Herpes Simplex Virus thymidine kinase (TK) gene or the bacterial xanthine-guanine phosphoribosyl-transferase (gpt) gene.

The gene targeting or gene activation techniques which can be used in accordance with this aspect of the invention are more particularly described in U.S. Patent No. 5,272,071 to Chappel; U.S. Patent No. 5,578,461 to Sherwin et al.; International Application No. PCT/US92/09627 (WO93/09222) by Selden et al.; and International Application No. PCT/US90/06436 (WO91/06667) by Skoultchi et al., each of which is incorporated by reference herein in its entirety.

#### 4.6 POLYPEPTIDES OF THE INVENTION

The isolated polypeptides of the invention include, but are not limited to, a polypeptide comprising: the amino acid sequences set forth as any one of SEQ ID NO:237-472 and 709-944 or an amino acid sequence encoded by any one of the nucleotide sequences SEO ID NO:1-236 and 473-708 or the corresponding full length or mature protein. Polypeptides of the invention also include polypeptides preferably with biological or immunological activity that are encoded by: (a) a polynucleotide having any one of the nucleotide sequences set forth in SEQ ID NO:1-236 and 473-708 or (b) polynucleotides encoding any one of the amino acid sequences set forth

as SEQ ID NO:237-472 and 709-944 or (c) polynucleotides that hybridize to the complement of the polynucleotides of either (a) or (b) under stringent hybridization conditions. The invention also provides biologically active or immunologically active variants of any of the amino acid sequences set forth as SEQ ID NO:237-472 and 709-944 or the corresponding full length or mature protein; and "substantial equivalents" thereof (e.g., with at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, typically at least about 95%, more typically at least about 98%, or most typically at least about 99% amino acid identity) that retain biological activity. Polypeptides encoded by allelic variants may have a similar, increased, or decreased activity compared to polypeptides comprising SEQ ID NO:237-472 and 709-944.

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Fragments of the proteins of the present invention which are capable of exhibiting biological activity are also encompassed by the present invention. Fragments of the protein may be in linear form or they may be cyclized using known methods, for example, as described in H. U. Saragovi, et al., Bio/Technology 10, 773-778 (1992) and in R. S. McDowell, et al., J. Amer. Chem. Soc. 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of protein binding sites.

The present invention also provides both full-length and mature forms (for example, without a signal sequence or precursor sequence) of the disclosed proteins. The protein coding sequence is identified in the sequence listing by translation of the disclosed nucleotide sequences. The mature form of such protein may be obtained by expression of a full-length polynucleotide in a suitable mammalian cell or other host cell. The sequence of the mature form of the protein is also determinable from the amino acid sequence of the full-length form. Where proteins of the present invention are membrane bound, soluble forms of the proteins are also provided. In such forms, part or all of the regions causing the proteins to be membrane bound are deleted so that the proteins are fully secreted from the cell in which they are expressed.

Protein compositions of the present invention may further comprise an acceptable carrier, such as a hydrophilic, e.g., pharmaceutically acceptable, carrier.

The present invention further provides isolated polypeptides encoded by the nucleic acid fragments of the present invention or by degenerate variants of the nucleic acid fragments of the present invention. By "degenerate variant" is intended nucleotide fragments which differ from a nucleic acid fragment of the present invention (e.g., an ORF) by nucleotide sequence but, due to the degeneracy of the genetic code, encode an identical polypeptide sequence. Preferred nucleic acid fragments of the present invention are the ORFs that encode proteins.

A variety of methodologies known in the art can be utilized to obtain any one of the isolated polypeptides or proteins of the present invention. At the simplest level, the amino acid sequence can be synthesized using commercially available peptide synthesizers. The synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith, including protein activity. This technique is particularly useful in producing small peptides and fragments of larger polypeptides. Fragments are useful, for example, in generating antibodies against the native polypeptide. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological processes for the development of antibodies.

The polypeptides and proteins of the present invention can alternatively be purified from cells which have been altered to express the desired polypeptide or protein. As used herein, a cell is said to be altered to express a desired polypeptide or protein when the cell, through genetic manipulation, is made to produce a polypeptide or protein which it normally does not produce or which the cell normally produces at a lower level. One skilled in the art can readily adapt procedures for introducing and expressing either recombinant or synthetic sequences into eukaryotic or prokaryotic cells in order to generate a cell which produces one of the polypeptides or proteins of the present invention.

The invention also relates to methods for producing a polypeptide comprising growing a culture of host cells of the invention in a suitable culture medium, and purifying the protein from the cells or the culture in which the cells are grown. For example, the methods of the invention include a process for producing a polypeptide in which a host cell containing a suitable expression vector that includes a polynucleotide of the invention is cultured under conditions that allow expression of the encoded polypeptide. The polypeptide can be recovered from the culture, conveniently from the culture medium, or from a lysate prepared from the host cells and further purified. Preferred embodiments include those in which the protein produced by such process is a full length or mature form of the protein.

In an alternative method, the polypeptide or protein is purified from bacterial cells which naturally produce the polypeptide or protein. One skilled in the art can readily follow known methods for isolating polypeptides and proteins in order to obtain one of the isolated polypeptides or proteins of the present invention. These include, but are not limited to, immunochromatography, HPLC, size-exclusion chromatography, ion-exchange chromatography, and immuno-affinity chromatography. See, e.g., Scopes, Protein Purification: Principles and Practice, Springer-Verlag (1994); Sambrook, et al., in Molecular Cloning: A Laboratory Manual; Ausubel et al., Current Protocols in Molecular Biology. Polypeptide fragments that

retain biological/immunological activity include fragments comprising greater than about 100 amino acids, or greater than about 200 amino acids, and fragments that encode specific protein domains.

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The purified polypeptides can be used in *in vitro* binding assays which are well known in the art to identify molecules which bind to the polypeptides. These molecules include but are not limited to, for e.g., small molecules, molecules from combinatorial libraries, antibodies or other proteins. The molecules identified in the binding assay are then tested for antagonist or agonist activity in *in vivo* tissue culture or animal models that are well known in the art. In brief, the molecules are titrated into a plurality of cell cultures or animals and then tested for either cell/animal death or prolonged survival of the animal/cells.

In addition, the peptides of the invention or molecules capable of binding to the peptides may be complexed with toxins, e.g., ricin or cholera, or with other compounds that are toxic to cells. The toxin-binding molecule complex is then targeted to a tumor or other cell by the specificity of the binding molecule for SEQ ID NO:237-472 and 709-944.

The protein of the invention may also be expressed as a product of transgenic animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are naturally provided or deliberately engineered. For example, modifications, in the peptide or DNA sequence, can be made by those skilled in the art using known techniques. Modifications of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or replaced with another amino acid to alter the conformation of the molecule. Techniques for such alteration, substitution, replacement, insertion or deletion are well known to those skilled in the art (see, e.g., U.S. Pat. No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity of the protein. Regions of the protein that are important for the protein function can be determined by various methods known in the art including the alanine-scanning method which involved systematic substitution of single or strings of amino acids with alanine, followed by testing the resulting alanine-containing variant for biological activity. This type of analysis determines the importance of the substituted amino acid(s) in biological activity. Regions of the protein that are important for protein function may be determined by the eMATRIX program.

Other fragments and derivatives of the sequences of proteins which would be expected to retain protein activity in whole or in part and are useful for screening or other immunological

methodologies may also be easily made by those skilled in the art given the disclosures herein. Such modifications are encompassed by the present invention.

The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, e.g., Invitrogen, San Diego, Calif., U.S.A. (the MaxBat<sup>TM</sup> kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

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The protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (i.e., from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column containing agents which will bind to the protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin-toyopearl<sup>TM</sup> or Cibacrom blue 3GA Sepharose<sup>TM</sup>; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

Alternatively, the protein of the invention may also be expressed in a form which will facilitate purification. For example, it may be expressed as a fusion protein, such as those of maltose binding protein (MBP), glutathione-S-transferase (GST) or thioredoxin (TRX), or as a His tag. Kits for expression and purification of such fusion proteins are commercially available from New England BioLab (Beverly, Mass.), Pharmacia (Piscataway, N.J.) and Invitrogen, respectively. The protein can also be tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope. One such epitope ("FLAG®") is commercially available from Kodak (New Haven, Conn.).

Finally, one or more reverse-phase high performance liquid chromatography (RP- HPLC) steps employing hydrophobic RP-HPLC media, e.g., silica gel having pendant methyl or other aliphatic groups, can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance with the present invention as an "isolated protein."

The polypeptides of the invention include analogs (variants). This embraces fragments, as well as peptides in which one or more amino acids has been deleted, inserted, or substituted. Also, analogs of the polypeptides of the invention embrace fusions of the polypeptides or modifications of the polypeptides of the invention, wherein the polypeptide or analog is fused to another moiety or moieties, e.g., targeting moiety or another therapeutic agent. Such analogs may exhibit improved properties such as activity and/or stability. Examples of moieties which may be fused to the polypeptide or an analog include, for example, targeting moieties which provide for the delivery of polypeptide to pancreatic cells, e.g., antibodies to pancreatic cells, antibodies to immune cells such as T-cells, monocytes, dendritic cells, granulocytes, etc., as well as receptor and ligands expressed on pancreatic or immune cells. Other moieties which may be fused to the polypeptide include therapeutic agents which are used for treatment, for example, immunosuppressive drugs such as cyclosporin, SK506, azathioprine, CD3 antibodies and steroids. Also, polypeptides may be fused to immune modulators, and other cytokines such as alpha or beta interferon.

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# 4.6.1 DETERMINING POLYPEPTIDE AND POLYNUCLEOTIDE IDENTITY AND SIMILARITY

Preferred identity and/or similarity are designed to give the largest match between the sequences tested. Methods to determine identity and similarity are codified in computer programs including, but are not limited to, the GCG program package, including GAP (Devereux, J., et al., Nucleic Acids Research 12(1):387 (1984); Genetics Computer Group, University of Wisconsin, Madison, WI), BLASTP, BLASTN, BLASTX, FASTA (Altschul, S.F. et al., J. Molec. Biol. 215:403-410 (1990), PSI-BLAST (Altschul S.F. et al., Nucleic Acids Res. vol. 25, pp. 3389-3402, herein incorporated by reference), eMatrix software (Wu et al., J. Comp. Biol., Vol. 6, pp. 219-235 (1999), herein incorporated by reference), eMotif software (Nevill-Manning et al, ISMB-97, Vol. 4, pp. 202-209, herein incorporated by reference), pFam software (Sonnhammer et al., Nucleic Acids Res., Vol. 26(1), pp. 320-322 (1998), herein incorporated by reference) and the Kyte-Doolittle hydrophobocity prediction algorithm (J. Mol Biol, 157, pp. 105-31 (1982), incorporated herein by reference). The BLAST programs are publicly available from the National Center for Biotechnology Information (NCBI) and other sources (BLAST Manual, Altschul, S., et al. NCB NLM NIH Bethesda, MD 20894; Altschul, S., et al., J. Mol. Biol. 215:403-410 (1990).

# 4.7 CHIMERIC AND FUSION PROTEINS

The invention also provides chimeric or fusion proteins. As used herein, a "chimeric protein" or "fusion protein" comprises a polypeptide of the invention operatively linked to

another polypeptide. Within a fusion protein the polypeptide according to the invention can correspond to all or a portion of a protein according to the invention. In one embodiment, a fusion protein comprises at least one biologically active portion of a protein according to the invention. In another embodiment, a fusion protein comprises at least two biologically active portions of a protein according to the invention. Within the fusion protein, the term "operatively linked" is intended to indicate that the polypeptide according to the invention and the other polypeptide are fused in-frame to each other. The polypeptide can be fused to the N-terminus or C-terminus.

For example, in one embodiment a fusion protein comprises a polypeptide according to the invention operably linked to the extracellular domain of a second protein.

In another embodiment, the fusion protein is a GST-fusion protein in which the polypeptide sequences of the invention are fused to the C-terminus of the GST (i.e., glutathione S-transferase) sequences.

In another embodiment, the fusion protein is an immunoglobulin fusion protein in which the polypeptide sequences according to the invention comprise one or more domains fused to sequences derived from a member of the immunoglobulin protein family. The immunoglobulin fusion proteins of the invention can be incorporated into pharmaceutical compositions and administered to a subject to inhibit an interaction between a ligand and a protein of the invention on the surface of a cell, to thereby suppress signal transduction *in vivo*. The immunoglobulin fusion proteins can be used to affect the bioavailability of a cognate ligand. Inhibition of the ligand/protein interaction may be useful therapeutically for both the treatment of proliferative and differentiative disorders, *e,g.*, cancer as well as modulating (*e.g.*, promoting or inhibiting) cell survival. Moreover, the immunoglobulin fusion proteins of the invention can be used as immunogens to produce antibodies in a subject, to purify ligands, and in screening assays to identify molecules that inhibit the interaction of a polypeptide of the invention with a ligand.

A chimeric or fusion protein of the invention can be produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different polypeptide sequences are ligated together in-frame in accordance with conventional techniques, e.g., by employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers.

Alternatively, PCR amplification of gene fragments can be carried out using anchor primers that give rise to complementary overhangs between two consecutive gene fragments that can subsequently be annealed and reamplified to generate a chimeric gene sequence (see, for

example, Ausubel et al. (eds.) CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (e.g., a GST polypeptide). A nucleic acid encoding a polypeptide of the invention can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the protein of the invention.

#### 4.8 GENE THERAPY

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Mutations in the polynucleotides of the invention gene may result in loss of normal function of the encoded protein. The invention thus provides gene therapy to restore normal activity of the polypeptides of the invention; or to treat disease states involving polypeptides of the invention. Delivery of a functional gene encoding polypeptides of the invention to appropriate cells is effected ex vivo, in situ, or in vivo by use of vectors, and more particularly viral vectors (e.g., adenovirus, adeno-associated virus, or a retrovirus), or ex vivo by use of physical DNA transfer methods (e.g., liposomes or chemical treatments). See, for example, Anderson, Nature, supplement to vol. 392, no. 6679, pp.25-20 (1998). For additional reviews of gene therapy technology see Friedmann, Science, 244: 1275-1281 (1989); Verma, Scientific American: 68-84 (1990); and Miller, Nature, 357: 455-460 (1992). Introduction of any one of the nucleotides of the present invention or a gene encoding the polypeptides of the present invention can also be accomplished with extrachromosomal substrates (transient expression) or artificial chromosomes (stable expression). Cells may also be cultured ex vivo in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced in vivo for therapeutic purposes. Alternatively, it is contemplated that in other human disease states, preventing the expression of or inhibiting the activity of polypeptides of the invention will be useful in treating the disease states. It is contemplated that antisense therapy or gene therapy could be applied to negatively regulate the expression of polypeptides of the invention.

Other methods inhibiting expression of a protein include the introduction of antisense molecules to the nucleic acids of the present invention, their complements, or their translated RNA sequences, by methods known in the art. Further, the polypeptides of the present invention can be inhibited by using targeted deletion methods, or the insertion of a negative regulatory element such as a silencer, which is tissue specific.

The present invention still further provides cells genetically engineered *in vivo* to express the polynucleotides of the invention, wherein such polynucleotides are in operative association with a regulatory sequence heterologous to the host cell which drives expression of the polynucleotides in

the cell. These methods can be used to increase or decrease the expression of the polynucleotides of the present invention.

Knowledge of DNA sequences provided by the invention allows for modification of cells to permit, increase, or decrease, expression of endogenous polypeptide. Cells can be modified (e.g., by homologous recombination) to provide increased polypeptide expression by replacing, in whole or in part, the naturally occurring promoter with all or part of a heterologous promoter so that the cells express the protein at higher levels. The heterologous promoter is inserted in such a manner that it is operatively linked to the desired protein encoding sequences. See, for example, PCT International Publication No. WO 94/12650, PCT International Publication No. WO 92/20808, and PCT International Publication No. WO 91/09955. It is also contemplated that, in addition to heterologous promoter DNA, amplifiable marker DNA (e.g., ada, dhfr, and the multifunctional CAD gene which encodes carbamyl phosphate synthase, aspartate transcarbamylase, and dihydroorotase) and/or intron DNA may be inserted along with the heterologous promoter DNA. If linked to the desired protein coding sequence, amplification of the marker DNA by standard selection methods results in co-amplification of the desired protein coding sequences in the cells.

In another embodiment of the present invention, cells and tissues may be engineered to express an endogenous gene comprising the polynucleotides of the invention under the control of inducible regulatory elements, in which case the regulatory sequences of the endogenous gene may be replaced by homologous recombination. As described herein, gene targeting can be used to replace a gene's existing regulatory region with a regulatory sequence isolated from a different gene or a novel regulatory sequence synthesized by genetic engineering methods. Such regulatory sequences may be comprised of promoters, enhancers, scaffold-attachment regions, negative regulatory elements, transcriptional initiation sites, regulatory protein binding sites or combinations of said sequences. Alternatively, sequences which affect the structure or stability of the RNA or protein produced may be replaced, removed, added, or otherwise modified by targeting. These sequences include polyadenylation signals, mRNA stability elements, splice sites, leader sequences for enhancing or modifying transport or secretion properties of the protein, or other sequences which alter or improve the function or stability of protein or RNA molecules.

The targeting event may be a simple insertion of the regulatory sequence, placing the gene under the control of the new regulatory sequence, e.g., inserting a new promoter or enhancer or both upstream of a gene. Alternatively, the targeting event may be a simple deletion of a regulatory element, such as the deletion of a tissue-specific negative regulatory element. Alternatively, the targeting event may replace an existing element; for example, a tissue-specific enhancer can be replaced by an enhancer that has broader or different cell-type specificity than the naturally occurring elements. Here, the naturally occurring sequences are deleted and new sequences are

added. In all cases, the identification of the targeting event may be facilitated by the use of one or more selectable marker genes that are contiguous with the targeting DNA, allowing for the selection of cells in which the exogenous DNA has integrated into the cell genome. The identification of the targeting event may also be facilitated by the use of one or more marker genes exhibiting the property of negative selection, such that the negatively selectable marker is linked to the exogenous DNA, but configured such that the negatively selectable marker flanks the targeting sequence, and such that a correct homologous recombination event with sequences in the host cell genome does not result in the stable integration of the negatively selectable marker. Markers useful for this purpose include the Herpes Simplex Virus thymidine kinase (TK) gene or the bacterial xanthine-guanine phosphoribosyl-transferase (gpt) gene.

The gene targeting or gene activation techniques which can be used in accordance with this aspect of the invention are more particularly described in U.S. Patent No. 5,272,071 to Chappel; U.S. Patent No. 5,578,461 to Sherwin et al.; International Application No. PCT/US92/09627 (WO93/09222) by Selden et al.; and International Application No. PCT/US90/06436 (WO91/06667) by Skoultchi et al., each of which is incorporated by reference herein in its entirety.

## 4.9 TRANSGENIC ANIMALS

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In preferred methods to determine biological functions of the polypeptides of the invention in vivo, one or more genes provided by the invention are either over expressed or inactivated in the germ line of animals using homologous recombination [Capecchi, Science 244:1288-1292 (1989)]. Animals in which the gene is over expressed, under the regulatory control of exogenous or endogenous promoter elements, are known as transgenic animals. Animals in which an endogenous gene has been inactivated by homologous recombination are referred to as "knockout" animals. Knockout animals, preferably non-human mammals, can be prepared as described in U.S. Patent No. 5,557,032, incorporated herein by reference. Transgenic animals are useful to determine the roles polypeptides of the invention play in biological processes, and preferably in disease states. Transgenic animals are useful as model systems to identify compounds that modulate lipid metabolism. Transgenic animals, preferably non-human mammals, are produced using methods as described in U.S. Patent No 5,489,743 and PCT Publication No. WO94/28122, incorporated herein by reference.

Transgenic animals can be prepared wherein all or part of a promoter of the polynucleotides of the invention is either activated or inactivated to alter the level of expression of the polypeptides of the invention. Inactivation can be carried out using homologous recombination methods described above. Activation can be achieved by supplementing or even replacing the homologous promoter to provide for increased protein expression. The homologous

promoter can be supplemented by insertion of one or more heterologous enhancer elements known to confer promoter activation in a particular tissue.

The polynucleotides of the present invention also make possible the development, through, e.g., homologous recombination or knock out strategies, of animals that fail to express polypeptides of the invention or that express a variant polypeptide. Such animals are useful as models for studying the *in vivo* activities of polypeptide as well as for studying modulators of the polypeptides of the invention.

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In preferred methods to determine biological functions of the polypeptides of the invention *in vivo*, one or more genes provided by the invention are either over expressed or inactivated in the germ line of animals using homologous recombination [Capecchi, Science 244:1288-1292 (1989)]. Animals in which the gene is over expressed, under the regulatory control of exogenous or endogenous promoter elements, are known as transgenic animals. Animals in which an endogenous gene has been inactivated by homologous recombination are referred to as "knockout" animals. Knockout animals, preferably non-human mammals, can be prepared as described in U.S. Patent No. 5,557,032, incorporated herein by reference. Transgenic animals are useful to determine the roles polypeptides of the invention play in biological processes, and preferably in disease states. Transgenic animals are useful as model systems to identify compounds that modulate lipid metabolism. Transgenic animals, preferably non-human mammals, are produced using methods as described in U.S. Patent No 5,489,743 and PCT Publication No. WO94/28122, incorporated herein by reference.

Transgenic animals can be prepared wherein all or part of the polynucleotides of the invention promoter is either activated or inactivated to alter the level of expression of the polypeptides of the invention. Inactivation can be carried out using homologous recombination methods described above. Activation can be achieved by supplementing or even replacing the homologous promoter to provide for increased protein expression. The homologous promoter can be supplemented by insertion of one or more heterologous enhancer elements known to confer promoter activation in a particular tissue.

#### 4.10 USES AND BIOLOGICAL ACTIVITY

The polynucleotides and proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified herein. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA). The mechanism underlying the particular condition or pathology will dictate whether the

polypeptides of the invention, the polynucleotides of the invention or modulators (activators or inhibitors) thereof would be beneficial to the subject in need of treatment. Thus, "therapeutic compositions of the invention" include compositions comprising isolated polynucleotides (including recombinant DNA molecules, cloned genes and degenerate variants thereof) or polypeptides of the invention (including full length protein, mature protein and truncations or domains thereof), or compounds and other substances that modulate the overall activity of the target gene products, either at the level of target gene/protein expression or target protein activity. Such modulators include polypeptides, analogs, (variants), including fragments and fusion proteins, antibodies and other binding proteins; chemical compounds that directly or indirectly activate or inhibit the polypeptides of the invention (identified, e.g., via drug screening assays as described herein); antisense polynucleotides and polynucleotides suitable for triple helix formation; and in particular antibodies or other binding partners that specifically recognize one or more epitopes of the polypeptides of the invention.

The polypeptides of the present invention may likewise be involved in cellular activation or in one of the other physiological pathways described herein.

#### 4.10.1 RESEARCH USES AND UTILITIES

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The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The polypeptides provided by the present invention can similarly be used in assays to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding polypeptide is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E. F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S. L. and A. R. Kimmel eds., 1987.

#### 4.10.2 NUTRITIONAL USES

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Polynucleotides and polypeptides of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the polypeptide or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the polypeptide or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

# 4.10.3 CYTOKINE AND CELL PROLIFERATION/DIFFERENTIATION ACTIVITY

A polypeptide of the present invention may exhibit activity relating to cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. A polynucleotide of the invention can encode a polypeptide exhibiting such attributes. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor-dependent cell proliferation assays, and hence the assays serve as a convenient

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confirmation of cytokine activity. The activity of therapeutic compositions of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+(preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e, CMK, HUVEC, and Caco. Therapeutic compositions of the invention can be used in the following:

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Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans): Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., I. Immunol. 149:3778-3783, 1992; Bowman et al., I. Immunol. 152:1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A. M. and Shevach, E. M. In Current Protocols in Immunology. J. E. e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human interleukin-y, Schreiber, R. D. In Current Protocols in Immunology. J. E. e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L. S. and Lipsky, P. E. In Current Protocols in Immunology. J. E. e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6--Nordan, R. In Current Protocols in Immunology. J. E. Coligan eds. Vol 25 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Aced. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11--Bennett, F., Giannotti, J., Clark, S. C. and Turner, K. J. In Current Protocols in Immunology. J. E. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9--Ciarletta, A., Giannotti, J., Clark, S. C. and Turner, K. J. In Current Protocols in Immunology. 30 J. E. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, W Strober,

Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, *In Vitro* assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

#### 4.10.4 STEM CELL GROWTH FACTOR ACTIVITY

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A polypeptide of the present invention may exhibit stem cell growth factor activity and be involved in the proliferation, differentiation and survival of pluripotent and totipotent stem cells including primordial germ cells, embryonic stem cells, hematopoietic stem cells and/or germ line stem cells. Administration of the polypeptide of the invention to stem cells *in vivo* or *ex vivo* is expected to maintain and expand cell populations in a totipotential or pluripotential state which would be useful for re-engineering damaged or diseased tissues, transplantation, manufacture of bio-pharmaceuticals and the development of bio-sensors. The ability to produce large quantities of human cells has important working applications for the production of human proteins which currently must be obtained from non-human sources or donors, implantation of cells to treat diseases such as Parkinson's, Alzheimer's and other neurodegenerative diseases; tissues for grafting such as bone marrow, skin, cartilage, tendons, bone, muscle (including cardiac muscle), blood vessels, cornea, neural cells, gastrointestinal cells and others; and organs for transplantation such as kidney, liver, pancreas (including islet cells), heart and lung.

It is contemplated that multiple different exogenous growth factors and/or cytokines may be administered in combination with the polypeptide of the invention to achieve the desired effect, including any of the growth factors listed herein, other stem cell maintenance factors, and specifically including stem cell factor (SCF), leukemia inhibitory factor (LIF), Flt-3 ligand (Flt-3L), any of the interleukins, recombinant soluble IL-6 receptor fused to IL-6, macrophage inflammatory protein 1-alpha (MIP-1-alpha), G-CSF, GM-CSF, thrombopoietin (TPO), platelet factor 4 (PF-4), platelet-derived growth factor (PDGF), neural growth factors and basic fibroblast growth factor (bFGF).

Since totipotent stem cells can give rise to virtually any mature cell type, expansion of these cells in culture will facilitate the production of large quantities of mature cells. Techniques for culturing stem cells are known in the art and administration of polypeptides of the invention, optionally with other growth factors and/or cytokines, is expected to enhance the survival and proliferation of the stem cell populations. This can be accomplished by direct administration of the polypeptide of the invention to the culture medium. Alternatively, stroma cells transfected with a polynucleotide that encodes for the polypeptide of the invention can be used as a feeder

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layer for the stem cell populations in culture or in vivo. Stromal support cells for feeder layers may include embryonic bone marrow fibroblasts, bone marrow stromal cells, fetal liver cells, or cultured embryonic fibroblasts (see U.S. Patent No. 5,690,926).

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Stem cells themselves can be transfected with a polynucleotide of the invention to induce autocrine expression of the polypeptide of the invention. This will allow for generation of undifferentiated totipotential/pluripotential stem cell lines that are useful as is or that can then be differentiated into the desired mature cell types. These stable cell lines can also serve as a source of undifferentiated totipotential/pluripotential mRNA to create cDNA libraries and templates for polymerase chain reaction experiments. These studies would allow for the isolation and identification of differentially expressed genes in stem cell populations that regulate stem cell proliferation and/or maintenance.

Expansion and maintenance of totipotent stem cell populations will be useful in the treatment of many pathological conditions. For example, polypeptides of the present invention may be used to manipulate stem cells in culture to give rise to neuroepithelial cells that can be used to augment or replace cells damaged by illness, autoimmune disease, accidental damage or genetic disorders. The polypeptide of the invention may be useful for inducing the proliferation of neural cells and for the regeneration of nerve and brain tissue, i.e. for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders which involve degeneration, death or trauma to neural cells or nerve tissue. In addition, the expanded stem cell populations can also be genetically altered for gene therapy purposes and to decrease host rejection of replacement tissues after grafting or implantation.

Expression of the polypeptide of the invention and its effect on stem cells can also be manipulated to achieve controlled differentiation of the stem cells into more differentiated cell types. A broadly applicable method of obtaining pure populations of a specific differentiated cell type from undifferentiated stem cell populations involves the use of a cell-type specific promoter driving a selectable marker. The selectable marker allows only cells of the desired type to survive. For example, stem cells can be induced to differentiate into cardiomyocytes (Wobus et al., Differentiation, 48: 173-182, (1991); Klug et al., J. Clin. Invest., 98(1): 216-224, (1998)) or skeletal muscle cells (Browder, L. W. In: *Principles of Tissue Engineering eds*. Lanza et al., Academic Press (1997)). Alternatively, directed differentiation of stem cells can be accomplished by culturing the stem cells in the presence of a differentiation factor such as retinoic acid and an antagonist of the polypeptide of the invention which would inhibit the effects of endogenous stem cell factor activity and allow differentiation to proceed.

In vitro cultures of stem cells can be used to determine if the polypeptide of the invention exhibits stem cell growth factor activity. Stem cells are isolated from any one of various cell

sources (including hematopoietic stem cells and embryonic stem cells) and cultured on a feeder layer, as described by Thompson et al. Proc. Natl. Acad. Sci, U.S.A., 92: 7844-7848 (1995), in the presence of the polypeptide of the invention alone or in combination with other growth factors or cytokines. The ability of the polypeptide of the invention to induce stem cells proliferation is determined by colony formation on semi-solid support e.g. as described by Bernstein et al., Blood, 77: 2316-2321 (1991).

## 4.10.5 HEMATOPOIESIS REGULATING ACTIVITY

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A polypeptide of the present invention may be involved in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell disorders. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or ex-vivo (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

Therapeutic compositions of the invention can be used in the following:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M. G. In Culture of Hematopoietic Cells. R. I. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, N.Y. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells 5 with high proliferative potential, McNiece, I. K. and Briddell, R. A. In Culture of Hematopoietic Cells. R. I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, N.Y. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R. E. In Culture of Hematopoietic Cells. R. I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc., New York, N.Y. 1994; Long term bone marrow cultures in the presence of 10 stromal cells, Spooncer, E., Dexter, M. and Allen, T. In Culture of Hematopoietic Cells. R. I. Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, N.Y. 1994; Long term culture initiating cell assay, Sutherland, H. J. In Culture of Hematopoietic Cells. R. I. Freshney, et al. eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, N.Y. 1994.

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## 4.10.6 TISSUE GROWTH ACTIVITY

A polypeptide of the present invention also may be involved in bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as in wound healing and tissue repair and replacement, and in healing of burns, incisions and ulcers.

A polypeptide of the present invention which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Compositions of a polypeptide, antibody, binding partner, or other modulator of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A polypeptide of this invention may also be involved in attracting bone-forming cells, stimulating growth of bone-forming cells, or inducing differentiation of progenitors of bone-forming cells. Treatment of osteoporosis, osteoarthritis, bone degenerative disorders, or periodontal disease, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes may also be possible using the composition of the invention.

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Another category of tissue regeneration activity that may involve the polypeptide of the present invention is tendon/ligament formation. Induction of tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect tissue repair. The compositions of the invention may also be useful in the 15 . treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The compositions of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, i.e. for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a composition may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a composition of the invention.

Compositions of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

Compositions of the present invention may also be involved in the generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine,

kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring may allow normal tissue to regenerate. A polypeptide of the present invention may also exhibit angiogenic activity.

A composition of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A composition of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

Therapeutic compositions of the invention can be used in the following:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, H. I. and Rovee, D. T., eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

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# 4.10.7 IMMUNE STIMULATING OR SUPPRESSING ACTIVITY

A polypeptide of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A polynucleotide of the invention can encode a polypeptide exhibiting such activities. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases causes by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpes viruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, proteins of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

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Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein (or antagonists thereof, including antibodies) of the present invention may also to be useful in the treatment of allergic reactions and conditions (e.g., anaphylaxis, serum sickness, drug reactions, food allergies, insect venom allergies, mastocytosis, allergic rhinitis, hypersensitivity pneumonitis, urticaria, angioedema, eczema, atopic dermatitis, allergic contact dermatitis, erythema multiforme, Stevens-Johnson syndrome, allergic conjunctivitis, atopic keratoconjunctivitis, venereal keratoconjunctivitis, giant papillary conjunctivitis and contact allergies), such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein (or antagonists thereof) of the present invention. The therapeutic effects of the polypeptides or antagonists thereof on allergic reactions can be evaluated by in vivo animals models such as the cumulative contact enhancement test (Lastborn et al., Toxicology 125: 59-66, 1998), skin prick test (Hoffmann et al., Allergy 54: 446-54, 1999), guinea pig skin sensitization test (Vohr et al., Arch. Toxocol. 73: 501-9), and murine local lymph node assay (Kimber et al., J. Toxicol. Environ. Health 53: 563-79).

Using the proteins of the invention it may also be possible to modulate immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as, for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue

transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a therapeutic composition of the invention may prevent cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, a lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular therapeutic compositions in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of therapeutic compositions of the invention on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block stimulation of T cells can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/lpr/lpr mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (e.g., a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial

immune response. For example, enhancing an immune response may be useful in cases of viral infection, including systemic viral diseases such as influenza, the common cold, and encephalitis.

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Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells in vivo.

A polypeptide of the present invention may provide the necessary stimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient mounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I alpha chain protein and β₂ microglobulin protein or an MHC class II alpha chain protein and an MHC class II beta chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J.

Immunol. 135:1564-1572, 1985; Takai et al., I. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bowman et al., J. Virology 61:1992-1998; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: In vitro antibody production, Mond, J. J. and Brunswick, M. In Current Protocols in Immunology. J. E. e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

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Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

### 4.10.8 ACTIVIN/INHIBIN ACTIVITY

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A polypeptide of the present invention may also exhibit activin- or inhibin-related activities. A polynucleotide of the invention may encode a polypeptide exhibiting such characteristics. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a polypeptide of the present invention, alone or in heterodimers with a member of the inhibin family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the polypeptide of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, U.S. Pat. No. 4,798,885. A polypeptide of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as, but not limited to, cows, sheep and pigs.

The activity of a polypeptide of the invention may, among other means, be measured by the following methods.

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

## 4.10.9 CHEMOTACTIC/CHEMOKINETIC ACTIVITY

A polypeptide of the present invention may be involved in chemotactic or chemokinetic activity for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. A polynucleotide of the invention can encode a polypeptide exhibiting such attributes. Chemotactic and chemokinetic receptor activation can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic compositions (e.g. proteins, antibodies, binding partners, or modulators of the invention) provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

Therapeutic compositions of the invention can be used in the following:

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Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Marguiles, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25:1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153:1762-1768, 1994.

# 4.10.10 HEMOSTATIC AND THROMBOLYTIC ACTIVITY

A polypeptide of the invention may also be involved in hemostatis or thrombolysis or thrombosis. A polynucleotide of the invention can encode a polypeptide exhibiting such attributes. Compositions may be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A composition of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

Therapeutic compositions of the invention can be used in the following:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

## 4.10.11 CANCER DIAGNOSIS AND THERAPY

Polypeptides of the invention may be involved in cancer cell generation, proliferation or metastasis. Detection of the presence or amount of polynucleotides or polypeptides of the

invention may be useful for the diagnosis and/or prognosis of one or more types of cancer. For example, the presence or increased expression of a polynucleotide/polypeptide of the invention may indicate a hereditary risk of cancer, a precancerous condition, or an ongoing malignancy. Conversely, a defect in the gene or absence of the polypeptide may be associated with a cancer condition. Identification of single nucleotide polymorphisms associated with cancer or a predisposition to cancer may also be useful for diagnosis or prognosis.

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Cancer treatments promote tumor regression by inhibiting tumor cell proliferation, inhibiting angiogenesis (growth of new blood vessels that is necessary to support tumor growth) and/or prohibiting metastasis by reducing tumor cell motility or invasiveness. Therapeutic compositions of the invention may be effective in adult and pediatric oncology including in solid phase tumors/malignancies, locally advanced tumors, human soft tissue sarcomas, metastatic cancer, including lymphatic metastases, blood cell malignancies including multiple myeloma, acute and chronic leukemias, and lymphomas, head and neck cancers including mouth cancer, larynx cancer and thyroid cancer, lung cancers including small cell carcinoma and non-small cell cancers, breast cancers including small cell carcinoma and ductal carcinoma, gastrointestinal cancers including esophageal cancer, stomach cancer, colon cancer, colorectal cancer and polyps associated with colorectal neoplasia, pancreatic cancers, liver cancer, urologic cancers including bladder cancer and prostate cancer, malignancies of the female genital tract including ovarian carcinoma, uterine (including endometrial) cancers, and solid tumor in the ovarian follicle, kidney cancers including renal cell carcinoma, brain cancers including intrinsic brain tumors, neuroblastoma, astrocytic brain tumors, gliomas, metastatic tumor cell invasion in the central nervous system, bone cancers including osteomas, skin cancers including malignant melanoma, tumor progression of human skin keratinocytes, squamous cell carcinoma, basal cell carcinoma, hemangiopericytoma and Karposi's sarcoma.

Polypeptides, polynucleotides, or modulators of polypeptides of the invention (including inhibitors and stimulators of the biological activity of the polypeptide of the invention) may be administered to treat cancer. Therapeutic compositions can be administered in therapeutically effective dosages alone or in combination with adjuvant cancer therapy such as surgery, chemotherapy, radiotherapy, thermotherapy, and laser therapy, and may provide a beneficial effect, e.g. reducing tumor size, slowing rate of tumor growth, inhibiting metastasis, or otherwise improving overall clinical condition, without necessarily eradicating the cancer.

The composition can also be administered in therapeutically effective amounts as a portion of an anti-cancer cocktail. An anti-cancer cocktail is a mixture of the polypeptide or modulator of the invention with one or more anti-cancer drugs in addition to a pharmaceutically acceptable carrier for delivery. The use of anti-cancer cocktails as a cancer treatment is routine.

Anti-cancer drugs that are well known in the art and can be used as a treatment in combination with the polypeptide or modulator of the invention include: Actinomycin D, Aminoglutethimide, Asparaginase, Bleomycin, Busulfan, Carboplatin, Carmustine, Chlorambucil, Cisplatin (cisDDP), Cyclophosphamide, Cytarabine HCl (Cytosine arabinoside), Dacarbazine, Dactinomycin,
Daunorubicin HCl, Doxorubicin HCl, Estramustine phosphate sodium, Etoposide (V16-213), Floxuridine, 5-Fluorouracil (5-Fu), Flutamide, Hydroxyurea (hydroxycarbamide), Ifosfamide, Interferon Alpha-2a, Interferon Alpha-2b, Leuprolide acetate (LHRH-releasing factor analog), Lomustine, Mechlorethamine HCl (nitrogen mustard), Melphalan, Mercaptopurine, Mesna, Methotrexate (MTX), Mitomycin, Mitoxantrone HCl, Octreotide, Plicamycin, Procarbazine HCl,
Streptozocin, Tamoxifen citrate, Thioguanine, Thiotepa, Vinblastine sulfate, Vincristine sulfate, Amsacrine, Azacitidine, Hexamethylmelamine, Interleukin-2, Mitoguazone, Pentostatin, Semustine, Teniposide, and Vindesine sulfate.

In addition, therapeutic compositions of the invention may be used for prophylactic treatment of cancer. There are hereditary conditions and/or environmental situations (e.g. exposure to carcinogens) known in the art that predispose an individual to developing cancers. Under these circumstances, it may be beneficial to treat these individuals with therapeutically effective doses of the polypeptide of the invention to reduce the risk of developing cancers.

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In vitro models can be used to determine the effective doses of the polypeptide of the invention as a potential cancer treatment. These in vitro models include proliferation assays of cultured tumor cells, growth of cultured tumor cells in soft agar (see Freshney, (1987) Culture of Animal Cells: A Manual of Basic Technique, Wily-Liss, New York, NY Ch 18 and Ch 21), tumor systems in nude mice as described in Giovanella et al., J. Natl. Can. Inst., 52: 921-30 (1974), mobility and invasive potential of tumor cells in Boyden Chamber assays as described in Pilkington et al., Anticancer Res., 17: 4107-9 (1997), and angiogenesis assays such as induction of vascularization of the chick chorioallantoic membrane or induction of vascular endothelial cell migration as described in Ribatta et al., Intl. J. Dev. Biol., 40: 1189-97 (1999) and Li et al., Clin. Exp. Metastasis, 17:423-9 (1999), respectively. Suitable tumor cells lines are available, e.g. from American Type Tissue Culture Collection catalogs.

## 4.10.12 RECEPTOR/LIGAND ACTIVITY

A polypeptide of the present invention may also demonstrate activity as receptor, receptor ligand or inhibitor or agonist of receptor/ligand interactions. A polynucleotide of the invention can encode a polypeptide exhibiting such characteristics. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions

and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses. Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a polypeptide of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley- Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

By way of example, the polypeptides of the invention may be used as a receptor for a ligand(s) thereby transmitting the biological activity of that ligand(s). Ligands may be identified through binding assays, affinity chromatography, dihybrid screening assays, BIAcore assays, gel overlay assays, or other methods known in the art.

Studies characterizing drugs or proteins as agonist or antagonist or partial agonists or a partial antagonist require the use of other proteins as competing ligands. The polypeptides of the present invention or ligand(s) thereof may be labeled by being coupled to radioisotopes, colorimetric molecules or a toxin molecules by conventional methods. ("Guide to Protein Purification" Murray P. Deutscher (ed) Methods in Enzymology Vol. 182 (1990) Academic Press, Inc. San Diego). Examples of radioisotopes include, but are not limited to, tritium and carbon-14. Examples of colorimetric molecules include, but are not limited to, fluorescent molecules such as fluorescamine, or rhodamine or other colorimetric molecules. Examples of toxins include, but are not limited, to ricin.

## 4.10.13 DRUG SCREENING

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This invention is particularly useful for screening chemical compounds by using the novel polypeptides or binding fragments thereof in any of a variety of drug screening techniques. The polypeptides or fragments employed in such a test may either be free in solution, affixed to a solid support, borne on a cell surface or located intracellularly. One method of drug screening

utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or a fragment thereof. Drugs are screened against such transformed cells in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, the formation of complexes between polypeptides of the invention or fragments and the agent being tested or examine the diminution in complex formation between the novel polypeptides and an appropriate cell line, which are well known in the art.

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Sources for test compounds that may be screened for ability to bind to or modulate (i.e., increase or decrease) the activity of polypeptides of the invention include (1) inorganic and organic chemical libraries, (2) natural product libraries, and (3) combinatorial libraries comprised of either random or mimetic peptides, oligonucleotides or organic molecules.

Chemical libraries may be readily synthesized or purchased from a number of commercial sources, and may include structural analogs of known compounds or compounds that are identified as "hits" or "leads" via natural product screening.

The sources of natural product libraries are microorganisms (including bacteria and fungi), animals, plants or other vegetation, or marine organisms, and libraries of mixtures for screening may be created by: (1) fermentation and extraction of broths from soil, plant or marine microorganisms or (2) extraction of the organisms themselves. Natural product libraries include polyketides, non-ribosomal peptides, and (non-naturally occurring) variants thereof. For a review, see *Science 282*:63-68 (1998).

Combinatorial libraries are composed of large numbers of peptides, oligonucleotides or organic compounds and can be readily prepared by traditional automated synthesis methods, PCR, cloning or proprietary synthetic methods. Of particular interest are peptide and oligonucleotide combinatorial libraries. Still other libraries of interest include peptide, protein, peptidomimetic, multiparallel synthetic collection, recombinatorial, and polypeptide libraries. For a review of combinatorial chemistry and libraries created therefrom, see Myers, Curr. Opin. Biotechnol. 8:701-707 (1997). For reviews and examples of peptidomimetic libraries, see Al-Obeidi et al., Mol. Biotechnol, 9(3):205-23 (1998); Hruby et al., Curr Opin Chem Biol, 1(1):114-19 (1997); Dorner et al., Bioorg Med Chem, 4(5):709-15 (1996) (alkylated dipeptides).

Identification of modulators through use of the various libraries described herein permits modification of the candidate "hit" (or "lead") to optimize the capacity of the "hit" to bind a polypeptide of the invention. The molecules identified in the binding assay are then tested for antagonist or agonist activity in *in vivo* tissue culture or animal models that are well known in the art. In brief, the molecules are titrated into a plurality of cell cultures or animals and then tested for either cell/animal death or prolonged survival of the animal/cells.

The binding molecules thus identified may be complexed with toxins, e.g., ricin or cholera, or with other compounds that are toxic to cells such as radioisotopes. The toxin-binding molecule complex is then targeted to a tumor or other cell by the specificity of the binding molecule for a polypeptide of the invention. Alternatively, the binding molecules may be complexed with imaging agents for targeting and imaging purposes.

### 4.10.14 ASSAY FOR RECEPTOR ACTIVITY

The invention also provides methods to detect specific binding of a polypeptide e.g. a ligand or a receptor. The art provides numerous assays particularly useful for identifying previously unknown binding partners for receptor polypeptides of the invention. For example, expression cloning using mammalian or bacterial cells, or dihybrid screening assays can be used to identify polynucleotides encoding binding partners. As another example, affinity chromatography with the appropriate immobilized polypeptide of the invention can be used to isolate polypeptides that recognize and bind polypeptides of the invention. There are a number of different libraries used for the identification of compounds, and in particular small molecules. that modulate (i.e., increase or decrease) biological activity of a polypeptide of the invention. Ligands for receptor polypeptides of the invention can also be identified by adding exogenous ligands, or cocktails of ligands to two cells populations that are genetically identical except for the expression of the receptor of the invention: one cell population expresses the receptor of the invention whereas the other does not. The response of the two cell populations to the addition of ligands(s) are then compared. Alternatively, an expression library can be co-expressed with the polypeptide of the invention in cells and assayed for an autocrine response to identify potential ligand(s). As still another example, BIAcore assays, gel overlay assays, or other methods known in the art can be used to identify binding partner polypeptides, including, (1) organic and inorganic chemical libraries, (2) natural product libraries, and (3) combinatorial libraries comprised of random peptides, oligonucleotides or organic molecules.

The role of downstream intracellular signaling molecules in the signaling cascade of the polypeptide of the invention can be determined. For example, a chimeric protein in which the cytoplasmic domain of the polypeptide of the invention is fused to the extracellular portion of a protein, whose ligand has been identified, is produced in a host cell. The cell is then incubated with the ligand specific for the extracellular portion of the chimeric protein, thereby activating the chimeric receptor. Known downstream proteins involved in intracellular signaling can then be assayed for expected modifications i.e. phosphorylation. Other methods known to those in the art can also be used to identify signaling molecules involved in receptor activity.

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## 4.10.15 ANTI-INFLAMMATORY ACTIVITY

Compositions of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Compositions with such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation intimation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Compositions of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material. Compositions of this invention may be utilized to prevent or treat conditions such as, but not limited to, sepsis, acute pancreatitis, endotoxin shock, cytokine induced shock, rheumatoid arthritis, chronic inflammatory arthritis, pancreatic cell damage from diabetes mellitus type 1, graft versus host disease, inflammatory bowel disease, inflamation associated with pulmonary disease, other autoimmune disease or inflammatory disease, an antiproliferative agent such as for acute or chronic mylegenous leukemia or in the prevention of premature labor secondary to intrauterine infections.

#### **4.10.16 LEUKEMIAS**

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Leukemias and related disorders may be treated or prevented by administration of a
therapeutic that promotes or inhibits function of the polynucleotides and/or polypeptides of the invention. Such leukemias and related disorders include but are not limited to acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, myeloblastic, promyelocytic, myelomonocytic, monocytic, erythroleukemia, chronic leukemia, chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia (for a review of such disorders, see
Fishman et al., 1985, Medicine, 2d Ed., J.B. Lippincott Co., Philadelphia).

#### 4.10.17 NERVOUS SYSTEM DISORDERS

Nervous system disorders, involving cell types which can be tested for efficacy of intervention with compounds that modulate the activity of the polynucleotides and/or polypeptides of the invention, and which can be treated upon thus observing an indication of

therapeutic utility, include but are not limited to nervous system injuries, and diseases or disorders which result in either a disconnection of axons, a diminution or degeneration of neurons, or demyelination. Nervous system lesions which may be treated in a patient (including human and non-human mammalian patients) according to the invention include but are not limited to the following lesions of either the central (including spinal cord, brain) or peripheral nervous systems:

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- (i) traumatic lesions, including lesions caused by physical injury or associated with surgery, for example, lesions which sever a portion of the nervous system, or compression injuries;
- (ii) ischemic lesions, in which a lack of oxygen in a portion of the nervous system results in neuronal injury or death, including cerebral infarction or ischemia, or spinal cord infarction or ischemia;
  - (iii) infectious lesions, in which a portion of the nervous system is destroyed or injured as a result of infection, for example, by an abscess or associated with infection by human immunodeficiency virus, herpes zoster, or herpes simplex virus or with Lyme disease, tuberculosis, syphilis;
  - (iv) degenerative lesions, in which a portion of the nervous system is destroyed or injured as a result of a degenerative process including but not limited to degeneration associated with Parkinson's disease, Alzheimer's disease, Huntington's chorea, or amyotrophic lateral sclerosis;
  - (v) lesions associated with nutritional diseases or disorders, in which a portion of the nervous system is destroyed or injured by a nutritional disorder or disorder of metabolism including but not limited to, vitamin B12 deficiency, folic acid deficiency, Wernicke disease, tobacco-alcohol amblyopia, Marchiafava-Bignami disease (primary degeneration of the corpus callosum), and alcoholic cerebellar degeneration;
  - (vi) neurological lesions associated with systemic diseases including but not limited to diabetes (diabetic neuropathy, Bell's palsy), systemic lupus erythematosus, carcinoma, or sarcoidosis;
- (vii) lesions caused by toxic substances including alcohol, lead, or particular
   neurotoxins; and
  - (viii) demyelinated lesions in which a portion of the nervous system is destroyed or injured by a demyelinating disease including but not limited to multiple sclerosis, human immunodeficiency virus-associated myelopathy, transverse myelopathy or various etiologies, progressive multifocal leukoencephalopathy, and central pontine myelinolysis.

Therapeutics which are useful according to the invention for treatment of a nervous system disorder may be selected by testing for biological activity in promoting the survival or differentiation of neurons. For example, and not by way of limitation, therapeutics which elicit any of the following effects may be useful according to the invention:

(i) increased survival time of neurons in culture;

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- (ii) increased sprouting of neurons in culture or in vivo;
- (iii) increased production of a neuron-associated molecule in culture or *in vivo*, *e.g.*, choline acetyltransferase or acetylcholinesterase with respect to motor neurons; or
  - (iv) decreased symptoms of neuron dysfunction in vivo.

Such effects may be measured by any method known in the art. In preferred, non-limiting embodiments, increased survival of neurons may be measured by the method set forth in Arakawa et al. (1990, J. Neurosci. 10:3507-3515); increased sprouting of neurons may be detected by methods set forth in Pestronk et al. (1980, Exp. Neurol. 70:65-82) or Brown et al. (1981, Ann. Rev. Neurosci. 4:17-42); increased production of neuron-associated molecules may be measured by bioassay, enzymatic assay, antibody binding, Northern blot assay, etc., depending on the molecule to be measured; and motor neuron dysfunction may be measured by assessing the physical manifestation of motor neuron disorder, e.g., weakness, motor neuron conduction velocity, or functional disability.

In specific embodiments, motor neuron disorders that may be treated according to the invention include but are not limited to disorders such as infarction, infection, exposure to toxin, trauma, surgical damage, degenerative disease or malignancy that may affect motor neurons as well as other components of the nervous system, as well as disorders that selectively affect neurons such as amyotrophic lateral sclerosis, and including but not limited to progressive spinal muscular atrophy, progressive bulbar palsy, primary lateral sclerosis, infantile and juvenile muscular atrophy, progressive bulbar paralysis of childhood (Fazio-Londe syndrome), poliomyelitis and the post polio syndrome, and Hereditary Motorsensory Neuropathy (Charcot-Marie-Tooth Disease).

#### 4.10.18 OTHER ACTIVITIES

A polypeptide of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape);

effecting biorhythms or circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, co-factors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

## 4.10.19 IDENTIFICATION OF POLYMORPHISMS

The demonstration of polymorphisms makes possible the identification of such polymorphisms in human subjects and the pharmacogenetic use of this information for diagnosis and treatment. Such polymorphisms may be associated with, e.g., differential predisposition or susceptibility to various disease states (such as disorders involving inflammation or immune response) or a differential response to drug administration, and this genetic information can be used to tailor preventive or therapeutic treatment appropriately. For example, the existence of a polymorphism associated with a predisposition to inflammation or autoimmune disease makes possible the diagnosis of this condition in humans by identifying the presence of the polymorphism.

Polymorphisms can be identified in a variety of ways known in the art which all generally involve obtaining a sample from a patient, analyzing DNA from the sample, optionally involving isolation or amplification of the DNA, and identifying the presence of the polymorphism in the DNA. For example, PCR may be used to amplify an appropriate fragment of genomic DNA which may then be sequenced. Alternatively, the DNA may be subjected to allele-specific oligonucleotide hybridization (in which appropriate oligonucleotides are hybridized to the DNA under conditions permitting detection of a single base mismatch) or to a single nucleotide extension assay (in which an oligonucleotide that hybridizes immediately adjacent to the position of the polymorphism is extended with one or more labeled nucleotides). In addition, traditional restriction fragment length polymorphism analysis (using restriction enzymes that provide differential digestion of the genomic DNA depending on the presence or

absence of the polymorphism) may be performed. Arrays with nucleotide sequences of the present invention can be used to detect polymorphisms. The array can comprise modified nucleotide sequences of the present invention in order to detect the nucleotide sequences of the present invention. In the alternative, any one of the nucleotide sequences of the present invention can be placed on the array to detect changes from those sequences.

Alternatively a polymorphism resulting in a change in the amino acid sequence could also be detected by detecting a corresponding change in amino acid sequence of the protein, e.g., by an antibody specific to the variant sequence.

## 4.10.20 ARTHRITIS AND INFLAMMATION

The immunosuppressive effects of the compositions of the invention against rheumatoid arthritis is determined in an experimental animal model system. The experimental model system is adjuvant induced arthritis in rats, and the protocol is described by J. Holoshitz, et at., 1983, Science, 219:56, or by B. Waksman et al., 1963, Int. Arch. Allergy Appl. Immunol., 23:129. Induction of the disease can be caused by a single injection, generally intradermally, of a suspension of killed Mycobacterium tuberculosis in complete Freund's adjuvant (CFA). The route of injection can vary, but rats may be injected at the base of the tail with an adjuvant mixture. The polypeptide is administered in phosphate buffered solution (PBS) at a dose of about 1-5 mg/kg. The control consists of administering PBS only.

The procedure for testing the effects of the test compound would consist of intradermally injecting killed Mycobacterium tuberculosis in CFA followed by immediately administering the test compound and subsequent treatment every other day until day 24. At 14, 15, 18, 20, 22, and 24 days after injection of Mycobacterium CFA, an overall arthritis score may be obtained as described by J. Holoskitz above. An analysis of the data would reveal that the test compound would have a dramatic affect on the swelling of the joints as measured by a decrease of the arthritis score.

#### 4.11 THERAPEUTIC METHODS

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The compositions (including polypeptide fragments, analogs, variants and antibodies or other binding partners or modulators including antisense polynucleotides) of the invention have numerous applications in a variety of therapeutic methods. Examples of therapeutic applications include, but are not limited to, those exemplified herein.

#### 4.11.1 **EXAMPLE**

One embodiment of the invention is the administration of an effective amount of the polypeptides or other composition of the invention to individuals affected by a disease or disorder that can be modulated by regulating the peptides of the invention. While the mode of administration is not particularly important, parenteral administration is preferred. An exemplary mode of administration is to deliver an intravenous bolus. The dosage of the polypeptides or other composition of the invention will normally be determined by the prescribing physician. It is to be expected that the dosage will vary according to the age, weight, condition and response of the individual patient. Typically, the amount of polypeptide administered per dose will be in the range of about 0.01µg/kg to 100 mg/kg of body weight, with the preferred dose being about 0.1µg/kg to 10 mg/kg of patient body weight. For parenteral administration, polypeptides of the invention will be formulated in an injectable form combined with a pharmaceutically acceptable parenteral vehicle. Such vehicles are well known in the art and examples include water, saline, Ringer's solution, dextrose solution, and solutions consisting of small amounts of the human serum albumin. The vehicle may contain minor amounts of additives that maintain the isotonicity and stability of the polypeptide or other active ingredient. The preparation of such solutions is within the skill of the art.

# 4.12 PHARMACEUTICAL FORMULATIONS AND ROUTES OF ADMINISTRATION

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A protein or other composition of the present invention (from whatever source derived, including without limitation from recombinant and non-recombinant sources and including antibodies and other binding partners of the polypeptides of the invention) may be administered to a patient in need, by itself, or in pharmaceutical compositions where it is mixed with suitable carriers or excipient(s) at doses to treat or ameliorate a variety of disorders. Such a composition may optionally contain (in addition to protein or other active ingredient and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the disease or disorder in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet-derived growth

factor (PDGF), transforming growth factors (TGF- $\alpha$  and TGF- $\beta$ ), insulin-like growth factor (IGF), as well as cytokines described herein.

The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or other active ingredient or complement its activity or use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein or other active ingredient of the invention, or to minimize side effects. Conversely, protein or other active ingredient of the present invention may be included in formulations of the particular clotting factor, cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects of the clotting factor, cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent (such as IL-1Ra, IL-1 Hy1, IL-1 Hy2, anti-TNF, corticosteroids, immunosuppressive agents). A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

As an alternative to being included in a pharmaceutical composition of the invention including a first protein, a second protein or a therapeutic agent may be concurrently administered with the first protein (e.g., at the same time, or at differing times provided that therapeutic concentrations of the combination of agents is achieved at the treatment site). Techniques for formulation and administration of the compounds of the instant application may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, latest edition. A therapeutically effective dose further refers to that amount of the compound sufficient to result in amelioration of symptoms, e.g., treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, a therapeutically effective dose refers to that ingredient alone. When applied to a combination, a therapeutically effective dose refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of protein or other active ingredient of the present invention is administered to a mammal having a condition to be treated. Protein or other active ingredient of the present invention may be administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co- administered with one or more cytokines, lymphokines or other

hematopoietic factors, protein or other active ingredient of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein or other active ingredient of the present invention in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

## 4.12.1 ROUTES OF ADMINISTRATION

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Suitable routes of administration may, for example, include oral, rectal, transmucosal, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections. Administration of protein or other active ingredient of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection. Intravenous administration to the patient is preferred.

Alternately, one may administer the compound in a local rather than systemic manner, for example, via injection of the compound directly into a arthritic joints or in fibrotic tissue, often in a depot or sustained release formulation. In order to prevent the scarring process frequently occurring as complication of glaucoma surgery, the compounds may be administered topically, for example, as eye drops. Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with a specific antibody, targeting, for example, arthritic or fibrotic tissue. The liposomes will be targeted to and taken up selectively by the afflicted tissue.

The polypeptides of the invention are administered by any route that delivers an effective dosage to the desired site of action. The determination of a suitable route of administration and an effective dosage for a particular indication is within the level of skill in the art. Preferably for wound treatment, one administers the therapeutic compound directly to the site. Suitable dosage ranges for the polypeptides of the invention can be extrapolated from these dosages or from similar studies in appropriate animal models. Dosages can then be adjusted as necessary by the clinician to provide maximal therapeutic benefit.

## 4.12.2 COMPOSITIONS/FORMULATIONS

Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in a conventional manner using one or more physiologically acceptable carriers

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comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. These pharmaceutical compositions may be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes. Proper formulation is dependent upon the route of administration chosen. When a therapeutically effective amount of protein or other active ingredient of the present invention is administered orally, protein or other active ingredient of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein or other active ingredient of the present invention, and preferably from about 25 to 90% protein or other active ingredient of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein or other active ingredient of the present invention, and preferably from about 1 to 50% protein or other active ingredient of the present invention.

When a therapeutically effective amount of protein or other active ingredient of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein or other active ingredient of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein or other active ingredient solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein or other active ingredient of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art. For injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

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For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained from a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration. For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch. The compounds may be formulated for parenteral

administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides. In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

A pharmaceutical carrier for the hydrophobic compounds of the invention is a co-solvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. The co-solvent system may be the VPD co-solvent system. VPD is a solution of 3% w/ν benzyl alcohol, 8% w/ν of the nonpolar surfactant polysorbate 80, and 65% w/ν polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD:5W) consists of VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of polysorbate 80; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g. polyvinyl pyπolidone; and other

sugars or polysaccharides may substitute for dextrose. Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater toxicity. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various types of sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein or other active ingredient stabilization may be employed.

The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols. Many of the active ingredients of the invention may be provided as salts with pharmaceutically compatible counter ions. Such pharmaceutically acceptable base addition salts are those salts which retain the biological effectiveness and properties of the free acids and which are obtained by reaction with inorganic or organic bases such as sodium hydroxide, magnesium hydroxide, ammonia, trialkylamine, dialkylamine, monoalkylamine, dibasic amino acids, sodium acetate, potassium benzoate, triethanol amine and the like.

The pharmaceutical composition of the invention may be in the form of a complex of the protein(s) or other active ingredient(s) of present invention along with protein or peptide antigens. The protein and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that can directly signal T cells. Alternatively antibodies able to bind surface immunoglobulin and other molecules on B cells as well as antibodies able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

The pharmaceutical composition of the invention may be in the form of a liposome in which protein of the present invention is combined, in addition to other pharmaceutically

acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithins, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent Nos. 4,235,871; 4,501,728; 4,837,028; and 4,737,323, all of which are incorporated herein by reference.

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The amount of protein or other active ingredient of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of protein or other active ingredient of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein or other active ingredient of the present invention and observe the patient's response. Larger doses of protein or other active ingredient of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01 µg to about 100 mg (preferably about 0.1 µg to about 10 mg, more preferably about 0.1 µg to about 1 mg) of protein or other active ingredient of the present invention per kg body weight. For compositions of the present invention which are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein or other active ingredient of the invention which may also optionally be included in the composition as described above, may alternatively or additionally, be administered simultaneously or sequentially with the composition in the methods of the invention. Preferably for bone and/or cartilage formation, the composition would include a matrix capable of delivering the protein-containing or other active ingredient-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

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The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalcium phosphate, hydroxyapatite, polylactic acid, polyglycolic acid and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxyapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalcium phosphate. The bioceramics may be altered in composition, such as in calcium-aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability. Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 wt %, preferably 1-10 wt % based on total formulation weight, which represents the amount necessary to prevent desorption of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells. In further compositions, proteins or other active ingredients of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), and insulin-like growth factor (IGF).

The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to humans, are desired

patients for such treatment with proteins or other active ingredients of the present invention. The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering various factors which modify the action of the proteins, e.g., amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (e.g., bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline labeling.

Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either in vivo or ex vivo into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including, without limitation, in the form of viral vectors or naked DNA). Cells may also be cultured ex vivo in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced in vivo for therapeutic purposes.

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### 4.12.3 EFFECTIVE DOSAGE

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. More specifically, a therapeutically effective amount means an amount effective to prevent development of or to alleviate the existing symptoms of the subject being treated. Determination of the effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from appropriate in vitro assays. For example, a dose can be formulated in animal models to achieve a circulating concentration range that can be used to more accurately determine useful doses in humans. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes the IC<sub>50</sub> as determined in cell culture (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of the protein's biological activity). Such information can be used to more accurately determine useful doses in humans.

A therapeutically effective dose refers to that amount of the compound that results in amelioration of symptoms or a prolongation of survival in a patient. Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED<sub>50</sub> (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD<sub>50</sub> and ED<sub>50</sub>. Compounds which exhibit high therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the  $ED_{50}$  with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. See, e.g., Fingl et al., 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p.1. Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the desired effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from in vitro data. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations.

Dosage intervals can also be determined using MEC value. Compounds should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%. In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

An exemplary dosage regimen for polypeptides or other compositions of the invention will be in the range of about 0.01  $\mu$ g/kg to 100 mg/kg of body weight daily, with the preferred dose being about 0.1  $\mu$ g/kg to 25 mg/kg of patient body weight daily, varying in adults and children. Dosing may be once daily, or equivalent doses may be delivered at longer or shorter intervals.

The amount of composition administered will, of course, be dependent on the subject being treated, on the subject's age and weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

#### 4.12.4 PACKAGING

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The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

### 4.13 ANTIBODIES

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Also included in the invention are antibodies to proteins, or fragments of proteins of the invention. The term "antibody" as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin (Ig) molecules, i.e., molecules that contain an antigen binding site that specifically binds (immunoreacts with) an antigen. Such antibodies include, but are not limited to, polyclonal, monoclonal, chimeric, single chain,  $F_{ab}$ ,  $F_{ab}$  and  $F_{(ab)2}$  fragments, and an  $F_{ab}$  expression library. In general, an antibody molecule obtained from humans relates to any of the classes IgG, IgM, IgA, IgE and IgD, which differ from one another by the nature of the heavy chain present in the molecule. Certain classes have subclasses as well, such as  $IgG_1$ ,  $IgG_2$ , and others. Furthermore, in humans, the light chain may be a kappa chain or a lambda chain. Reference herein to antibodies includes a reference to all such classes, subclasses and types of human antibody species.

An isolated related protein of the invention may be intended to serve as an antigen, or a portion or fragment thereof, and additionally can be used as an immunogen to generate antibodies that immunospecifically bind the antigen, using standard techniques for polyclonal and monoclonal antibody preparation. The full-length protein can be used or, alternatively, the invention provides antigenic peptide fragments of the antigen for use as immunogens. An antigenic peptide fragment comprises at least 6 amino acid residues of the amino acid sequence of the full length protein, such as an amino acid sequence shown in SEQ ID NO: 237, and encompasses an epitope thereof such that an antibody raised against the peptide forms a specific immune complex with the full length protein or with any fragment that contains the epitope. Preferably, the antigenic peptide comprises at least 10 amino acid residues, or at least 15 amino acid residues, or at least 20 amino acid residues, or at least 30 amino acid residues. Preferred epitopes encompassed by the antigenic peptide are regions of the protein that are located on its surface; commonly these are hydrophilic regions.

In certain embodiments of the invention, at least one epitope encompassed by the antigenic peptide is a region of -related protein that is located on the surface of the protein, e.g., a hydrophilic region. A hydrophobicity analysis of the human related protein sequence will

indicate which regions of a related protein are particularly hydrophilic and, therefore, are likely to encode surface residues useful for targeting antibody production. As a means for targeting antibody production, hydropathy plots showing regions of hydrophilicity and hydrophobicity may be generated by any method well known in the art, including, for example, the Kyte Doolittle or the Hopp Woods methods, either with or without Fourier transformation. See, e.g., Hopp and Woods, 1981, Proc. Nat. Acad. Sci. USA 78: 3824-3828; Kyte and Doolittle 1982, J. Mol. Biol. 157: 105-142, each of which is incorporated herein by reference in its entirety. Antibodies that are specific for one or more domains within an antigenic protein, or derivatives, fragments, analogs or homologs thereof, are also provided herein.

A protein of the invention, or a derivative, fragment, analog, homolog or ortholog thereof, may be utilized as an immunogen in the generation of antibodies that immunospecifically bind these protein components.

Various procedures known within the art may be used for the production of polyclonal or monoclonal antibodies directed against a protein of the invention, or against derivatives, fragments, analogs homologs or orthologs thereof (see, for example, Antibodies: A Laboratory Manual, Harlow E, and Lane D, 1988, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, incorporated herein by reference). Some of these antibodies are discussed below.

### 5.13.1 Polyclonal Antibodies

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For the production of polyclonal antibodies, various suitable host animals (e.g., rabbit, goat, mouse or other mammal) may be immunized by one or more injections with the native protein, a synthetic variant thereof, or a derivative of the foregoing. An appropriate immunogenic preparation can contain, for example, the naturally occurring immunogenic protein, a chemically synthesized polypeptide representing the immunogenic protein, or a recombinantly expressed immunogenic protein. Furthermore, the protein may be conjugated to a second protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include but are not limited to keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. The preparation can further include an adjuvant. Various adjuvants used to increase the immunological response include, but are not limited to, Freund's (complete and incomplete), mineral gels (e.g., aluminum hydroxide), surface active substances (e.g., lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, dinitrophenol, etc.), adjuvants usable in humans such as Bacille Calmette-Guerin and Corynebacterium parvum, or similar immunostimulatory agents. Additional examples of adjuvants which can be employed include MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate).

The polyclonal antibody molecules directed against the immunogenic protein can be isolated from the mammal (e.g., from the blood) and further purified by well known techniques, such as affinity chromatography using protein A or protein G, which provide primarily the IgG fraction of immune serum. Subsequently, or alternatively, the specific antigen which is the target of the immunoglobulin sought, or an epitope thereof, may be immobilized on a column to purify the immune specific antibody by immunoaffinity chromatography. Purification of immunoglobulins is discussed, for example, by D. Wilkinson (The Scientist, published by The Scientist, Inc., Philadelphia PA, Vol. 14, No. 8 (April 17, 2000), pp. 25-28).

### 10 5.13.2 Monoclonal Antibodies

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The term "monoclonal antibody" (MAb) or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one molecular species of antibody molecule consisting of a unique light chain gene product and a unique heavy chain gene product. In particular, the complementarity determining regions (CDRs) of the monoclonal antibody are identical in all the molecules of the population. MAbs thus contain an antigen binding site capable of immunoreacting with a particular epitope of the antigen characterized by a unique binding affinity for it.

Monoclonal antibodies can be prepared using hybridoma methods, such as those described by Kohler and Milstein, Nature, 256:495 (1975). In a hybridoma method, a mouse, hamster, or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes can be immunized in vitro. The immunizing agent will typically include the protein antigen, a fragment thereof or a fusion protein thereof. Generally, either peripheral blood lymphocytes are used if cells of human origin are desired, or spleen cells or lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, Monoclonal Antibodies: Principles and Practice, Academic Press, (1986) pp. 59-103). Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells can be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine ("HAT medium"), which substances prevent the growth of HGPRT-deficient cells.

Preferred immortalized cell lines are those that fuse efficiently, support stable high level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk Institute Cell Distribution Center, San Diego, California and the American Type Culture Collection, Manassas, Virginia. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor, J. Immunol., 133:3001 (1984); Brodeur et al., Monoclonal Antibody Production Techniques and Applications, Marcel Dekker, Inc., New York, (1987) pp. 51-63).

The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against the antigen. Preferably, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an in vitro binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques and assays are known in the art. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Pollard, Anal. Biochem., 107:220 (1980). Preferably, antibodies having a high degree of specificity and a high binding affinity for the target antigen are isolated.

After the desired hybridoma cells are identified, the clones can be subcloned by limiting dilution procedures and grown by standard methods. Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells can be grown in vivo as ascites in a mammal. The monoclonal antibodies secreted by the subclones can be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

The monoclonal antibodies can also be made by recombinant DNA methods, such as those described in U.S. Patent No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA can be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also can be modified, for

example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences (U.S. Patent No. 4,816,567; Morrison, Nature 368, 812-13 (1994)) or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

#### 5.13.2 Humanized Antibodies

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The antibodies directed against the protein antigens of the invention can further comprise humanized antibodies or human antibodies. These antibodies are suitable for administration to humans without engendering an immune response by the human against the administered immunoglobulin. Humanized forms of antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')2 or other antigenbinding subsequences of antibodies) that are principally comprised of the sequence of a human immunoglobulin, and contain minimal sequence derived from a non-human immunoglobulin. Humanization can be performed following the method of Winter and co-workers (Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-327 (1988); Verhoeyen et al., Science, 239:1534-1536 (1988)), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. (See also U.S. Patent No. 5,225,539.) In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies can also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the framework regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin (Jones et al., 1986; Riechmann et al., 1988; and Presta, Curr. Op. Struct. Biol., 2:593-596 (1992)).

### 5.13.3 Human Antibodies

Fully human antibodies relate to antibody molecules in which essentially the entire sequences of both the light chain and the heavy chain, including the CDRs, arise from human genes. Such antibodies are termed "human antibodies", or "fully human antibodies" herein.

Human monoclonal antibodies can be prepared by the trioma technique; the human B-cell hybridoma technique (see Kozbor, et al., 1983 Immunol Today 4: 72) and the EBV hybridoma technique to produce human monoclonal antibodies (see Cole, et al., 1985 In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96). Human monoclonal antibodies may be utilized in the practice of the present invention and may be produced by using human hybridomas (see Cote, et al., 1983. Proc Natl Acad Sci USA 80: 2026-2030) or by transforming human B-cells with Epstein Barr Virus in vitro (see Cole, et al., 1985 In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96).

In addition, human antibodies can also be produced using additional techniques, including phage display libraries (Hoogenboom and Winter, <u>J. Mol. Biol.</u>, <u>227</u>:381 (1991); Marks et al., <u>J. Mol. Biol.</u>, <u>222</u>:581 (1991)). Similarly, human antibodies can be made by introducing human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example, in U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, and in Marks et al. (<u>Bio/Technology 10</u>, 779-783 (1992)); Lonberg et al. (<u>Nature 368</u> 856-859 (1994)); Morrison (<u>Nature 368</u>, 812-13 (1994)); Fishwild et al.(<u>Nature Biotechnology 14</u>, 845-51 (1996)); Neuberger (<u>Nature Biotechnology 14</u>, 826 (1996)); and Lonberg and Huszar (<u>Intern. Rev. Immunol. 13</u> 65-93 (1995)).

Human antibodies may additionally be produced using transgenic nonhuman animals which are modified so as to produce fully human antibodies rather than the animal's endogenous antibodies in response to challenge by an antigen. (See PCT publication WO94/02602). The endogenous genes encoding the heavy and light immunoglobulin chains in the nonhuman host have been incapacitated, and active loci encoding human heavy and light chain immunoglobulins are inserted into the host's genome. The human genes are incorporated, for example, using yeast artificial chromosomes containing the requisite human DNA segments. An animal which provides all the desired modifications is then obtained as progeny by crossbreeding intermediate transgenic animals containing fewer than the full complement of the modifications. The preferred embodiment of such a nonhuman animal is a mouse, and is termed the Xenomouse<sup>TM</sup> as disclosed in PCT publications WO 96/33735 and WO 96/34096. This animal produces B cells which secrete fully human immunoglobulins. The antibodies can be obtained directly from the animal after immunization with an immunogen of interest, as, for example, a preparation of a polyclonal antibody, or alternatively from immortalized B cells derived from the animal, such as hybridomas producing monoclonal antibodies. Additionally, the genes encoding the

immunoglobulins with human variable regions can be recovered and expressed to obtain the antibodies directly, or can be further modified to obtain analogs of antibodies such as, for example, single chain Fv molecules.

An example of a method of producing a nonhuman host, exemplified as a mouse, lacking expression of an endogenous immunoglobulin heavy chain is disclosed in U.S. Patent No. 5,939,598. It can be obtained by a method including deleting the J segment genes from at least one endogenous heavy chain locus in an embryonic stem cell to prevent rearrangement of the locus and to prevent formation of a transcript of a rearranged immunoglobulin heavy chain locus, the deletion being effected by a targeting vector containing a gene encoding a selectable marker; and producing from the embryonic stem cell a transgenic mouse whose somatic and germ cells contain the gene encoding the selectable marker.

A method for producing an antibody of interest, such as a human antibody, is disclosed in U.S. Patent No. 5,916,771. It includes introducing an expression vector that contains a nucleotide sequence encoding a heavy chain into one mammalian host cell in culture, introducing an expression vector containing a nucleotide sequence encoding a light chain into another mammalian host cell, and fusing the two cells to form a hybrid cell. The hybrid cell expresses an antibody containing the heavy chain and the light chain.

In a further improvement on this procedure, a method for identifying a clinically relevant epitope on an immunogen, and a correlative method for selecting an antibody that binds immunospecifically to the relevant epitope with high affinity, are disclosed in PCT publication WO 99/53049.

## 5.13.4 Fab Fragments and Single Chain Antibodies

According to the invention, techniques can be adapted for the production of single-chain antibodies specific to an antigenic protein of the invention (see e.g., U.S. Patent No. 4,946,778). In addition, methods can be adapted for the construction of  $F_{ab}$  expression libraries (see e.g., Huse, et al., 1989 Science 246: 1275-1281) to allow rapid and effective identification of monoclonal  $F_{ab}$  fragments with the desired specificity for a protein or derivatives, fragments, analogs or homologs thereof. Antibody fragments that contain the idiotypes to a protein antigen may be produced by techniques known in the art including, but not limited to: (i) an  $F_{(ab)/2}$  fragment produced by pepsin digestion of an antibody molecule; (ii) an  $F_{ab}$  fragment generated by reducing the disulfide bridges of an  $F_{(ab)/2}$  fragment; (iii) an  $F_{ab}$  fragment generated by the treatment of the antibody molecule with papain and a reducing agent and (iv)  $F_v$  fragments.

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Bispecific antibodies are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for an antigenic protein of the invention. The second binding target is any other antigen, and advantageously is a cell-surface protein or receptor or receptor subunit.

Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy-chain/light-chain pairs, where the two heavy chains have different specificities (Milstein and Cuello, Nature, 305:537-539 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of ten different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule is usually accomplished by affinity chromatography steps. Similar procedures are disclosed in WO 93/08829, published 13 May 1993, and in Traunecker *et al.*, 1991 *EMBO J.*, 10:3655-3659.

Antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavy-chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light-chain binding present in at least one of the fusions. DNAs encoding the immunoglobulin heavy-chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. For further details of generating bispecific antibodies see, for example, Suresh et al., Methods in Enzymology, 121:210 (1986).

According to another approach described in WO 96/27011, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface comprises at least a part of the CH3 region of an antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (e.g. tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e.g. alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e.g. F(ab')<sub>2</sub> bispecific antibodies). Techniques for generating bispecific antibodies from antibody fragments have been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. Brennan et al., <u>Science</u> 229:81 (1985) describe a procedure

wherein intact antibodies are proteolytically cleaved to generate F(ab')<sub>2</sub> fragments. These fragments are reduced in the presence of the dithiol complexing agent sodium arsenite to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

Additionally, Fab' fragments can be directly recovered from E. coli and chemically coupled to form bispecific antibodies. Shalaby et al., J. Exp. Med. 175:217-225 (1992) describe the production of a fully humanized bispecific antibody F(ab')<sub>2</sub> molecule. Each Fab' fragment was separately secreted from E. coli and subjected to directed chemical coupling in vitro to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets.

Various techniques for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny et al., J. Immunol. 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger et al., Proc. Natl. Acad. Sci. USA 90:6444-6448 (1993) has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a heavy-chain variable domain (V<sub>H</sub>) connected to a light-chain variable domain (V<sub>L</sub>) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V<sub>H</sub> and V<sub>L</sub> domains of one fragment are forced to pair with the complementary V<sub>L</sub> and V<sub>H</sub> domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See, Gruber et al., J. Immunol. 152:5368 (1994).

Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared. Tutt et al., <u>J. Immunol.</u> 147:60 (1991). Exemplary bispecific antibodies can bind to two different epitopes, at least one of which originates in the protein antigen of the invention. Alternatively, an anti-antigenic arm of an immunoglobulin molecule can be combined with an arm which binds to a triggering molecule on

a leukocyte such as a T-cell receptor molecule (e.g. CD2, CD3, CD28, or B7), or Fc receptors for IgG (FcγR), such as FcγRI (CD64), FcγRII (CD32) and FcγRII (CD16) so as to focus cellular defense mechanisms to the cell expressing the particular antigen. Bispecific antibodies can also be used to direct cytotoxic agents to cells which express a particular antigen. These antibodies possess an antigen-binding arm and an arm which binds a cytotoxic agent or a radionuclide chelator, such as EOTUBE, DPTA, DOTA, or TETA. Another bispecific antibody of interest binds the protein antigen described herein and further binds tissue factor (TF).

### 5.13.6 Heteroconjugate Antibodies

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Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells (U.S. Patent No. 4,676,980), and for treatment of HIV infection (WO 91/00360; WO 92/200373; EP 03089). It is contemplated that the antibodies can be prepared in vitro using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins can be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate and those disclosed, for example, in U.S. Patent No. 4,676,980.

### 5.13.7 Effector Function Engineering

It can be desirable to modify the antibody of the invention with respect to effector function, so as to enhance, e.g., the effectiveness of the antibody in treating cancer. For example, cysteine residue(s) can be introduced into the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated can have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). See Caron et al., J. Exp Med., 176: 1191-1195 (1992) and Shopes, J. Immunol., 148: 2918-2922 (1992). Homodimeric antibodies with enhanced antitumor activity can also be prepared using heterobifunctional cross-linkers as described in Wolff et al. Cancer Research, 53: 2560-2565 (1993). Alternatively, an antibody can be engineered that has dual Fc regions and can thereby have enhanced complement lysis and ADCC capabilities. See Stevenson et al., Anti-Cancer Drug Design, 3: 219-230 (1989).

### 5.13.8 Immunoconjugates

The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (e.g., an enzymatically active toxin of

bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (i.e., a radioconjugate).

Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above. Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from Pseudomonas aeruginosa), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, Aleurites fordii proteins, dianthin proteins, Phytolaca americana proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include <sup>212</sup>Bi, <sup>131</sup>I, <sup>131</sup>In, <sup>90</sup>Y, and <sup>186</sup>Re.

Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutareldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al., Science, 238: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026.

In another embodiment, the antibody can be conjugated to a "receptor" (such streptavidin) for utilization in tumor pretargeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then administration of a "ligand" (e.g., avidin) that is in turn conjugated to a cytotoxic agent.

### 4.14 COMPUTER READABLE SEQUENCES

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In one application of this embodiment, a nucleotide sequence of the present invention can be recorded on computer readable media. As used herein, "computer readable media" refers to any medium which can be read and accessed directly by a computer. Such media include, but are not limited to: magnetic storage media, such as floppy discs, hard disc storage medium, and magnetic tape; optical storage media such as CD-ROM; electrical storage media such as RAM and ROM; and hybrids of these categories such as magnetic/optical storage media. A skilled

artisan can readily appreciate how any of the presently known computer readable mediums can be used to create a manufacture comprising computer readable medium having recorded thereon a nucleotide sequence of the present invention. As used herein, "recorded" refers to a process for storing information on computer readable medium. A skilled artisan can readily adopt any of the presently known methods for recording information on computer readable medium to generate manufactures comprising the nucleotide sequence information of the present invention.

A variety of data storage structures are available to a skilled artisan for creating a computer readable medium having recorded thereon a nucleotide sequence of the present invention. The choice of the data storage structure will generally be based on the means chosen to access the stored information. In addition, a variety of data processor programs and formats can be used to store the nucleotide sequence information of the present invention on computer readable medium. The sequence information can be represented in a word processing text file, formatted in commercially-available software such as WordPerfect and Microsoft Word, or represented in the form of an ASCII file, stored in a database application, such as DB2, Sybase, Oracle, or the like. A skilled artisan can readily adapt any number of data processor structuring formats (e.g. text file or database) in order to obtain computer readable medium having recorded thereon the nucleotide sequence information of the present invention.

By providing any of the nucleotide sequences SEQ ID NO:1-236 and 473-708 or a representative fragment thereof; or a nucleotide sequence at least 95% identical to any of the nucleotide sequences of SEQ ID NO:1-236 and 473-708 in computer readable form, a skilled artisan can routinely access the sequence information for a variety of purposes. Computer software is publicly available which allows a skilled artisan to access sequence information provided in a computer readable medium. The examples which follow demonstrate how software which implements the BLAST (Altschul et al., J. Mol. Biol. 215:403-410 (1990)) and BLAZE (Brutlag et al., Comp. Chem. 17:203-207 (1993)) search algorithms on a Sybase system is used to identify open reading frames (ORFs) within a nucleic acid sequence. Such ORFs may be protein encoding fragments and may be useful in producing commercially important proteins such as enzymes used in fermentation reactions and in the production of commercially useful metabolites.

As used herein, "a computer-based system" refers to the hardware means, software means, and data storage means used to analyze the nucleotide sequence information of the present invention. The minimum hardware means of the computer-based systems of the present invention comprises a central processing unit (CPU), input means, output means, and data storage means. A skilled artisan can readily appreciate that any one of the currently available computer-based systems are suitable for use in the present invention. As stated above, the

computer-based systems of the present invention comprise a data storage means having stored therein a nucleotide sequence of the present invention and the necessary hardware means and software means for supporting and implementing a search means. As used herein, "data storage means" refers to memory which can store nucleotide sequence information of the present invention, or a memory access means which can access manufactures having recorded thereon the nucleotide sequence information of the present invention.

As used herein, "search means" refers to one or more programs which are implemented on the computer-based system to compare a target sequence or target structural motif with the sequence information stored within the data storage means. Search means are used to identify fragments or regions of a known sequence which match a particular target sequence or target motif. A variety of known algorithms are disclosed publicly and a variety of commercially available software for conducting search means are and can be used in the computer-based systems of the present invention. Examples of such software includes, but is not limited to, Smith-Waterman, MacPattern (EMBL), BLASTN and BLASTA (NPOLYPEPTIDEIA). A skilled artisan can readily recognize that any one of the available algorithms or implementing software packages for conducting homology searches can be adapted for use in the present computer-based systems. As used herein, a "target sequence" can be any nucleic acid or amino acid sequence of six or more nucleotides or two or more amino acids. A skilled artisan can readily recognize that the longer a target sequence is, the less likely a target sequence will be present as a random occurrence in the database. The most preferred sequence length of a target sequence is from about 10 to 300 amino acids, more preferably from about 30 to 100 nucleotide residues. However, it is well recognized that searches for commercially important fragments, such as sequence fragments involved in gene expression and protein processing, may be of shorter length.

As used herein, "a target structural motif," or "target motif," refers to any rationally selected sequence or combination of sequences in which the sequence(s) are chosen based on a three-dimensional configuration which is formed upon the folding of the target motif. There are a variety of target motifs known in the art. Protein target motifs include, but are not limited to, enzyme active sites and signal sequences. Nucleic acid target motifs include, but are not limited to, promoter sequences, hairpin structures and inducible expression elements (protein binding sequences).

#### 4.15 TRIPLE HELIX FORMATION

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In addition, the fragments of the present invention, as broadly described, can be used to control gene expression through triple helix formation or antisense DNA or RNA, both of which

methods are based on the binding of a polynucleotide sequence to DNA or RNA.

Polynucleotides suitable for use in these methods are preferably 20 to 40 bases in length and are designed to be complementary to a region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 15241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense - Olmno, J. Neurochem. 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988)). Triple helix-formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques have been demonstrated to be effective in model systems. Information contained in the sequences of the present invention is necessary for the design of an antisense or triple helix oligonucleotide.

### 4.16 DIAGNOSTIC ASSAYS AND KITS

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The present invention further provides methods to identify the presence or expression of one of the ORFs of the present invention, or homolog thereof, in a test sample, using a nucleic acid probe or antibodies of the present invention, optionally conjugated or otherwise associated with a suitable label.

In general, methods for detecting a polynucleotide of the invention can comprise contacting a sample with a compound that binds to and forms a complex with the polynucleotide for a period sufficient to form the complex, and detecting the complex, so that if a complex is detected, a polynucleotide of the invention is detected in the sample. Such methods can also comprise contacting a sample under stringent hybridization conditions with nucleic acid primers that anneal to a polynucleotide of the invention under such conditions, and amplifying annealed polynucleotides, so that if a polynucleotide is amplified, a polynucleotide of the invention is detected in the sample.

In general, methods for detecting a polypeptide of the invention can comprise contacting a sample with a compound that binds to and forms a complex with the polypeptide for a period sufficient to form the complex, and detecting the complex, so that if a complex is detected, a polypeptide of the invention is detected in the sample.

In detail, such methods comprise incubating a test sample with one or more of the antibodies or one or more of the nucleic acid probes of the present invention and assaying for binding of the nucleic acid probes or antibodies to components within the test sample.

Conditions for incubating a nucleic acid probe or antibody with a test sample vary.

Incubation conditions depend on the format employed in the assay, the detection methods employed, and the type and nature of the nucleic acid probe or antibody used in the assay. One

skilled in the art will recognize that any one of the commonly available hybridization, amplification or immunological assay formats can readily be adapted to employ the nucleic acid probes or antibodies of the present invention. Examples of such assays can be found in Chard, T., An Introduction to Radioimmunoassay and Related Techniques, Elsevier Science Publishers, Amsterdam, The Netherlands (1986); Bullock, G.R. et al., Techniques in Immunocytochemistry, Academic Press, Orlando, FL Vol. 1 (1982), Vol. 2 (1983), Vol. 3 (1985); Tijssen, P., Practice and Theory of immunoassays: Laboratory Techniques in Biochemistry and Molecular Biology, Elsevier Science Publishers, Amsterdam, The Netherlands (1985). The test samples of the present invention include cells, protein or membrane extracts of cells, or biological fluids such as sputum, blood, serum, plasma, or urine. The test sample used in the above-described method will vary based on the assay format, nature of the detection method and the tissues, cells or extracts used as the sample to be assayed. Methods for preparing protein extracts or membrane extracts of cells are well known in the art and can be readily be adapted in order to obtain a sample which is compatible with the system utilized.

In another embodiment of the present invention, kits are provided which contain the necessary reagents to carry out the assays of the present invention. Specifically, the invention provides a compartment kit to receive, in close confinement, one or more containers which comprises: (a) a first container comprising one of the probes or antibodies of the present invention; and (b) one or more other containers comprising one or more of the following: wash reagents, reagents capable of detecting presence of a bound probe or antibody.

In detail, a compartment kit includes any kit in which reagents are contained in separate containers. Such containers include small glass containers, plastic containers or strips of plastic or paper. Such containers allows one to efficiently transfer reagents from one compartment to another compartment such that the samples and reagents are not cross-contaminated, and the agents or solutions of each container can be added in a quantitative fashion from one compartment to another. Such containers will include a container which will accept the test sample, a container which contains the antibodies used in the assay, containers which contain wash reagents (such as phosphate buffered saline, Tris-buffers, etc.), and containers which contain the reagents used to detect the bound antibody or probe. Types of detection reagents include labeled nucleic acid probes, labeled secondary antibodies, or in the alternative, if the primary antibody is labeled, the enzymatic, or antibody binding reagents which are capable of reacting with the labeled antibody. One skilled in the art will readily recognize that the disclosed probes and antibodies of the present invention can be readily incorporated into one of the established kit formats which are well known in the art.

### 4.17 MEDICAL IMAGING

The novel polypeptides and binding partners of the invention are useful in medical imaging of sites expressing the molecules of the invention (e.g., where the polypeptide of the invention is involved in the immune response, for imaging sites of inflammation or infection). See, e.g., Kunkel et al., U.S. Pat. NO. 5,413,778. Such methods involve chemical attachment of a labeling or imaging agent, administration of the labeled polypeptide to a subject in a pharmaceutically acceptable carrier, and imaging the labeled polypeptide *in vivo* at the target site.

### 10 4.18 SCREENING ASSAYS

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Using the isolated proteins and polynucleotides of the invention, the present invention further provides methods of obtaining and identifying agents which bind to a polypeptide encoded by an ORF corresponding to any of the nucleotide sequences set forth in SEQ ID NO:1-236 and 473-708, or bind to a specific domain of the polypeptide encoded by the nucleic acid. In detail, said method comprises the steps of:

- (a) contacting an agent with an isolated protein encoded by an ORF of the present invention, or nucleic acid of the invention; and
  - (b) determining whether the agent binds to said protein or said nucleic acid.

In general, therefore, such methods for identifying compounds that bind to a polynucleotide of the invention can comprise contacting a compound with a polynucleotide of the invention for a time sufficient to form a polynucleotide/compound complex, and detecting the complex, so that if a polynucleotide/compound complex is detected, a compound that binds to a polynucleotide of the invention is identified.

Likewise, in general, therefore, such methods for identifying compounds that bind to a polypeptide of the invention can comprise contacting a compound with a polypeptide of the invention for a time sufficient to form a polypeptide/compound complex, and detecting the complex, so that if a polypeptide/compound complex is detected, a compound that binds to a polynucleotide of the invention is identified.

Methods for identifying compounds that bind to a polypeptide of the invention can also comprise contacting a compound with a polypeptide of the invention in a cell for a time sufficient to form a polypeptide/compound complex, wherein the complex drives expression of a receptor gene sequence in the cell, and detecting the complex by detecting reporter gene sequence expression, so that if a polypeptide/compound complex is detected, a compound that binds a polypeptide of the invention is identified.

Compounds identified via such methods can include compounds which modulate the activity of a polypeptide of the invention (that is, increase or decrease its activity, relative to activity observed in the absence of the compound). Alternatively, compounds identified via such methods can include compounds which modulate the expression of a polynucleotide of the invention (that is, increase or decrease expression relative to expression levels observed in the absence of the compound). Compounds, such as compounds identified via the methods of the invention, can be tested using standard assays well known to those of skill in the art for their ability to modulate activity/expression.

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The agents screened in the above assay can be, but are not limited to, peptides, carbohydrates, vitamin derivatives, or other pharmaceutical agents. The agents can be selected and screened at random or rationally selected or designed using protein modeling techniques.

For random screening, agents such as peptides, carbohydrates, pharmaceutical agents and the like are selected at random and are assayed for their ability to bind to the protein encoded by the ORF of the present invention. Alternatively, agents may be rationally selected or designed. As used herein, an agent is said to be "rationally selected or designed" when the agent is chosen based on the configuration of the particular protein. For example, one skilled in the art can readily adapt currently available procedures to generate peptides, pharmaceutical agents and the like, capable of binding to a specific peptide sequence, in order to generate rationally designed antipeptide peptides, for example see Hurby et al., Application of Synthetic Peptides: Antisense Peptides," In Synthetic Peptides, A User's Guide, W.H. Freeman, NY (1992), pp. 289-307, and Kaspczak et al., Biochemistry 28:9230-8 (1989), or pharmaceutical agents, or the like.

In addition to the foregoing, one class of agents of the present invention, as broadly described, can be used to control gene expression through binding to one of the ORFs or EMFs of the present invention. As described above, such agents can be randomly screened or rationally designed/selected. Targeting the ORF or EMF allows a skilled artisan to design sequence specific or element specific agents, modulating the expression of either a single ORF or multiple ORFs which rely on the same EMF for expression control. One class of DNA binding agents are agents which contain base residues which hybridize or form a triple helix formation by binding to DNA or RNA. Such agents can be based on the classic phosphodiester, ribonucleic acid backbone, or can be a variety of sulfhydryl or polymeric derivatives which have base attachment capacity.

Agents suitable for use in these methods preferably contain 20 to 40 bases and are designed to be complementary to a region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560

(1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988)). Triple helix-formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques have been demonstrated to be effective in model systems. Information contained in the sequences of the present invention is necessary for the design of an antisense or triple helix oligonucleotide and other DNA binding agents.

Agents which bind to a protein encoded by one of the ORFs of the present invention can be used as a diagnostic agent. Agents which bind to a protein encoded by one of the ORFs of the present invention can be formulated using known techniques to generate a pharmaceutical composition.

### 4.19 USE OF NUCLEIC ACIDS AS PROBES

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Another aspect of the subject invention is to provide for polypeptide-specific nucleic acid hybridization probes capable of hybridizing with naturally occurring nucleotide sequences. The hybridization probes of the subject invention may be derived from any of the nucleotide sequences SEQ ID NO:1-236 and 473-708. Because the corresponding gene is only expressed in a limited number of tissues, a hybridization probe derived from of any of the nucleotide sequences SEQ ID NO:1-236 and 473-708 can be used as an indicator of the presence of RNA of cell type of such a tissue in a sample.

Any suitable hybridization technique can be employed, such as, for example, in situ hybridization. PCR as described in US Patents Nos. 4,683,195 and 4,965,188 provides additional uses for oligonucleotides based upon the nucleotide sequences. Such probes used in PCR may be of recombinant origin, may be chemically synthesized, or a mixture of both. The probe will comprise a discrete nucleotide sequence for the detection of identical sequences or a degenerate pool of possible sequences for identification of closely related genomic sequences.

Other means for producing specific hybridization probes for nucleic acids include the cloning of nucleic acid sequences into vectors for the production of mRNA probes. Such vectors are known in the art and are commercially available and may be used to synthesize RNA probes in vitro by means of the addition of the appropriate RNA polymerase as T7 or SP6 RNA polymerase and the appropriate radioactively labeled nucleotides. The nucleotide sequences may be used to construct hybridization probes for mapping their respective genomic sequences. The nucleotide sequence provided herein may be mapped to a chromosome or specific regions of a chromosome using well known genetic and/or chromosomal mapping techniques. These techniques include in situ hybridization, linkage analysis against known chromosomal markers, hybridization screening with libraries or flow-sorted chromosomal preparations specific to

known chromosomes, and the like. The technique of fluorescent in situ hybridization of chromosome spreads has been described, among other places, in Verma et al (1988) Human Chromosomes: A Manual of Basic Techniques, Pergamon Press, New York NY.

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Fluorescent in situ hybridization of chromosomal preparations and other physical chromosome mapping techniques may be correlated with additional genetic map data. Examples of genetic map data can be found in the 1994 Genome Issue of Science (265:1981f). Correlation between the location of a nucleic acid on a physical chromosomal map and a specific disease (or predisposition to a specific disease) may help delimit the region of DNA associated with that genetic disease. The nucleotide sequences of the subject invention may be used to detect differences in gene sequences between normal, carrier or affected individuals.

# 4.20 PREPARATION OF SUPPORT BOUND OLIGONUCLEOTIDES

Oligonucleotides, i.e., small nucleic acid segments, may be readily prepared by, for example, directly synthesizing the oligonucleotide by chemical means, as is commonly practiced using an automated oligonucleotide synthesizer.

Support bound oligonucleotides may be prepared by any of the methods known to those of skill in the art using any suitable support such as glass, polystyrene or Teflon. One strategy is to precisely spot oligonucleotides synthesized by standard synthesizers. Immobilization can be achieved using passive adsorption (Inouye & Hondo, (1990) J. Clin. Microbiol. 28(6) 1469-72); using UV light (Nagata et al., 1985; Dahlen et al., 1987; Morrissey & Collins, (1989) Mol. Cell Probes 3(2) 189-207) or by covalent binding of base modified DNA (Keller et al., 1988; 1989); all references being specifically incorporated herein.

Another strategy that may be employed is the use of the strong biotin-streptavidin interaction as a linker. For example, Broude *et al.* (1994) Proc. Natl. Acad. Sci. USA 91(8) 3072-6, describe the use of biotinylated probes, although these are duplex probes, that are immobilized on streptavidin-coated magnetic beads. Streptavidin-coated beads may be purchased from Dynal, Oslo. Of course, this same linking chemistry is applicable to coating any surface with streptavidin. Biotinylated probes may be purchased from various sources, such as, e.g., Operon Technologies (Alameda, CA).

Nunc Laboratories (Naperville, IL) is also selling suitable material that could be used. Nunc Laboratories have developed a method by which DNA can be covalently bound to the microwell surface termed Covalink NH. CovaLink NH is a polystyrene surface grafted with secondary amino groups (>NH) that serve as bridge-heads for further covalent coupling. CovaLink Modules may be purchased from Nunc Laboratories. DNA molecules may be bound to CovaLink exclusively at the

5'-end by a phosphoramidate bond, allowing immobilization of more than 1 pmol of DNA (Rasmussen et al., (1991) Anal. Biochem. 198(1) 138-42).

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The use of CovaLink NH strips for covalent binding of DNA molecules at the 5'-end has been described (Rasmussen et al., (1991). In this technology, a phosphoramidate bond is employed (Chu et al., (1983) Nucleic Acids Res. 11(8) 6513-29). This is beneficial as immobilization using only a single covalent bond is preferred. The phosphoramidate bond joins the DNA to the CovaLink NH secondary amino groups that are positioned at the end of spacer arms covalently grafted onto the polystyrene surface through a 2 nm long spacer arm. To link an oligonucleotide to CovaLink NH via an phosphoramidate bond, the oligonucleotide terminus must have a 5'-end phosphate group. It is, perhaps, even possible for biotin to be covalently bound to CovaLink and then streptavidin used to bind the probes.

More specifically, the linkage method includes dissolving DNA in water (7.5 ng/ul) and denaturing for 10 min. at 95°C and cooling on ice for 10 min. Ice-cold 0.1 M 1-methylimidazole, pH 7.0 (1-MeIm<sub>7</sub>), is then added to a final concentration of 10 mM 1-MeIm<sub>7</sub>. A ss DNA solution is then dispensed into CovaLink NH strips (75 ul/well) standing on ice.

Carbodiimide 0.2 M 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC), dissolved in 10 mM 1-MeIm<sub>7</sub>, is made fresh and 25 ul added per well. The strips are incubated for 5 hours at 50°C. After incubation the strips are washed using, e.g., Nunc-Immuno Wash; first the wells are washed 3 times, then they are soaked with washing solution for 5 min., and finally they are washed 3 times (where in the washing solution is 0.4 N NaOH, 0.25% SDS heated to 50°C).

It is contemplated that a further suitable method for use with the present invention is that described in PCT Patent Application WO 90/03382 (Southern & Maskos), incorporated herein by reference. This method of preparing an oligonucleotide bound to a support involves attaching a nucleoside 3'-reagent through the phosphate group by a covalent phosphodiester link to aliphatic hydroxyl groups carried by the support. The oligonucleotide is then synthesized on the supported nucleoside and protecting groups removed from the synthetic oligonucleotide chain under standard conditions that do not cleave the oligonucleotide from the support. Suitable reagents include nucleoside phosphoramidite and nucleoside hydrogen phosphorate.

An on-chip strategy for the preparation of DNA probe for the preparation of DNA probe arrays may be employed. For example, addressable laser-activated photodeprotection may be employed in the chemical synthesis of oligonucleotides directly on a glass surface, as described by Fodor *et al.* (1991) Science 251(4995) 767-73, incorporated herein by reference. Probes may also be immobilized on nylon supports as described by Van Ness *et al.* (1991) Nucleic Acids Res. 19(12) 3345-50; or linked to Teflon using the method of Duncan & Cavalier (1988) Anal. Biochem. 169(1) 104-8; all references being specifically incorporated herein.

To link an oligonucleotide to a nylon support, as described by Van Ness et al. (1991), requires activation of the nylon surface via alkylation and selective activation of the 5'-amine of oligonucleotides with cyanuric chloride.

One particular way to prepare support bound oligonucleotides is to utilize the light-generated synthesis described by Pease *et al.*, (1994) PNAS USA 91(11) 5022-6, incorporated herein by reference). These authors used current photolithographic techniques to generate arrays of immobilized oligonucleotide probes (DNA chips). These methods, in which light is used to direct the synthesis of oligonucleotide probes in high-density, miniaturized arrays, utilize photolabile 5'-protected *N*-acyl-deoxynucleoside phosphoramidites, surface linker chemistry and versatile combinatorial synthesis strategies. A matrix of 256 spatially defined oligonucleotide probes may be generated in this manner.

### 4.21 PREPARATION OF NUCLEIC ACID FRAGMENTS

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The nucleic acids may be obtained from any appropriate source, such as cDNAs, genomic DNA, chromosomal DNA, microdissected chromosome bands, cosmid or YAC inserts, and RNA, including mRNA without any amplification steps. For example, Sambrook *et al.* (1989) describes three protocols for the isolation of high molecular weight DNA from mammalian cells (p. 9.14-9.23).

DNA fragments may be prepared as clones in M13, plasmid or lambda vectors and/or prepared directly from genomic DNA or cDNA by PCR or other amplification methods. Samples may be prepared or dispensed in multiwell plates. About 100-1000 ng of DNA samples may be prepared in 2-500 ml of final volume.

The nucleic acids would then be fragmented by any of the methods known to those of skill in the art including, for example, using restriction enzymes as described at 9.24-9.28 of Sambrook et al. (1989), shearing by ultrasound and NaOH treatment.

Low pressure shearing is also appropriate, as described by Schriefer et al. (1990) Nucleic Acids Res. 18(24) 7455-6, incorporated herein by reference). In this method, DNA samples are passed through a small French pressure cell at a variety of low to intermediate pressures. A lever device allows controlled application of low to intermediate pressures to the cell. The results of these studies indicate that low-pressure shearing is a useful alternative to sonic and enzymatic DNA fragmentation methods.

One particularly suitable way for fragmenting DNA is contemplated to be that using the two base recognition endonuclease, CviJI, described by Fitzgerald et al. (1992) Nucleic Acids Res. 20(14) 3753-62. These authors described an approach for the rapid fragmentation and fractionation

of DNA into particular sizes that they contemplated to be suitable for shotgun cloning and sequencing.

The restriction endonuclease CviJI normally cleaves the recognition sequence PuGCPy between the G and C to leave blunt ends. Atypical reaction conditions, which alter the specificity of this enzyme (CviJI\*\*), yield a quasi-random distribution of DNA fragments form the small molecule pUC19 (2688 base pairs). Fitzgerald et al. (1992) quantitatively evaluated the randomness of this fragmentation strategy, using a CviJI\*\* digest of pUC19 that was size fractionated by a rapid gel filtration method and directly ligated, without end repair, to a lac Z minus M13 cloning vector. Sequence analysis of 76 clones showed that CviJI\*\* restricts pyGCPy and PuGCPu, in addition to PuGCPy sites, and that new sequence data is accumulated at a rate consistent with random fragmentation.

As reported in the literature, advantages of this approach compared to sonication and agarose gel fractionation include: smaller amounts of DNA are required (0.2-0.5 ug instead of 2-5 ug); and fewer steps are involved (no preligation, end repair, chemical extraction, or agarose gel electrophoresis and elution are needed

Irrespective of the manner in which the nucleic acid fragments are obtained or prepared, it is important to denature the DNA to give single stranded pieces available for hybridization. This is achieved by incubating the DNA solution for 2-5 minutes at 80-90°C. The solution is then cooled quickly to 2°C to prevent renaturation of the DNA fragments before they are contacted with the chip. Phosphate groups must also be removed from genomic DNA by methods known in the art.

#### 4.22 PREPARATION OF DNA ARRAYS

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Arrays may be prepared by spotting DNA samples on a support such as a nylon membrane. Spotting may be performed by using arrays of metal pins (the positions of which correspond to an array of wells in a microtiter plate) to repeated by transfer of about 20 nl of a DNA solution to a nylon membrane. By offset printing, a density of dots higher than the density of the wells is achieved. One to 25 dots may be accommodated in 1 mm², depending on the type of label used. By avoiding spotting in some preselected number of rows and columns, separate subsets (subarrays) may be formed. Samples in one subarray may be the same genomic segment of DNA (or the same gene) from different individuals, or may be different, overlapped genomic clones. Each of the subarrays may represent replica spotting of the same samples. In one example, a selected gene segment may be amplified from 64 patients. For each patient, the amplified gene segment may be in one 96-well plate (all 96 wells containing the same sample). A plate for each of the 64 patients is prepared. By using a 96-pin device, all samples may be spotted on one 8 x 12 cm membrane.

Subarrays may contain 64 samples, one from each patient. Where the 96 subarrays are identical, the dot span may be 1 mm<sup>2</sup> and there may be a 1 mm space between subarrays.

Another approach is to use membranes or plates (available from NUNC, Naperville, Illinois) which may be partitioned by physical spacers e.g. a plastic grid molded over the membrane, the grid being similar to the sort of membrane applied to the bottom of multiwell plates, or hydrophobic strips. A fixed physical spacer is not preferred for imaging by exposure to flat phosphor-storage screens or x-ray films.

The present invention is illustrated in the following examples. Upon consideration of the present disclosure, one of skill in the art will appreciate that many other embodiments and variations may be made in the scope of the present invention. Accordingly, it is intended that the broader aspects of the present invention not be limited to the disclosure of the following examples. The present invention is not to be limited in scope by the exemplified embodiments which are intended as illustrations of single aspects of the invention, and compositions and methods which are functionally equivalent are within the scope of the invention. Indeed, numerous modifications and variations in the practice of the invention are expected to occur to those skilled in the art upon consideration of the present preferred embodiments. Consequently, the only limitations which should be placed upon the scope of the invention are those which appear in the appended claims.

All references cited within the body of the instant specification are hereby incorporated by reference in their entirety.

### 5.0 EXAMPLES

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### **5.1.1 EXAMPLE 1**

### Novel Nucleic Acid Sequences Obtained From Various Libraries

A plurality of novel nucleic acids were obtained from cDNA libraries prepared from various human tissues and in some cases isolated from a genomic library derived from human chromosome using standard PCR, SBH sequence signature analysis and Sanger sequencing techniques. The inserts of the library were amplified with PCR using primers specific for the vector sequences which flank the inserts. Clones from cDNA libraries were spotted on nylon membrane filters and screened with oligonucleotide probes (e.g., 7-mers) to obtain signature sequences. The clones were clustered into groups of similar or identical sequences. Representative clones were selected for sequencing.

In some cases, the 5' sequence of the amplified inserts was then deduced using a typical Sanger sequencing protocol. PCR products were purified and subjected to fluorescent dye terminator cycle sequencing. Single pass gel sequencing was done using a 377 Applied Biosystems

(ABI) sequencer to obtain the novel nucleic acid sequences. In some cases RACE (Random Amplification of cDNA Ends) was performed to further extend the sequence in the 5' direction.

### 5.1.2 EXAMPLE 2

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### Assemblage of Novel Nucleic Acids

The contigs or nucleic acids of the present invention, designated as SEQ ID NO: 473-708 were assembled using an EST sequence as a seed. Then a recursive algorithm was used to extend the seed EST into an extended assemblage, by pulling additional sequences from different databases (i.e., Hyseq's database containing EST sequences, dbEST version 114, gb pri 114, and UniGene version 101) that belong to this assemblage. The algorithm terminated when there was no additional sequences from the above databases that would extend the assemblage. Inclusion of component sequences into the assemblage was based on a BLASTN hit to the extending assemblage with BLAST score greater than 300 and percent identity greater than 95%.

A polypeptide was predicted to be encoded by each of SEQ ID NO:473-708 as set forth below. The polypeptides was predicted using a software program called FASTY (available from <a href="http://fasta.bioch.virginia.edu">http://fasta.bioch.virginia.edu</a>) which selects a polypeptides based on a comparison of translated novel polynucleotide to known polynucleotides (W.R. Pearson, Methods in Enzymology, 183:63-98 (1990), herein incorporated by reference. The predicted polypeptides are shown in Table 7.

#### 5.2.2 EXAMPLE 3

### **Novel Nucleic Acids**

Using PHRAP (Univ. of Washington) or CAP4 (Paracel), a full length gene cDNA sequence and its corresponding protein sequence were generated from the assemblage. Any frame shifts and incorrect stop codons were corrected by hand editing. During editing, the sequence was checked using FASTY and/or BLAST against Genbank (i.e. dbEST version 117, gb pri 117, UniGene version 117, Genpept release 117). Other computer programs which may have been used in the editing process were phredPhrap and Consed (University of Washington) and ed-ready, edext and gc-zip-2 (Hyseq, Inc.). The full-length nucleotide, including splice variants resulting from these procedures are shown in the Sequence Listing as SEQ ID NOS:1-217.

Table 1 shows the various tissue sources of SEQ ID NO: 1-217.

The nearest neighbor results for SEQ ID NO: 1-217 were obtained by a BLASTP version 2.0al 19MP-WashU search against Genpept release 120 and Geneseq October 12, 2000 release 21 (Derwent), using BLAST algorithm. The nearest neighbor result showed the closest homologue for SEQ ID NO: 1-217 from Genpept. The translated amino acid sequences for which the nucleic acid sequence encodes are shown in the Sequence Listing. The homologs with identifiable functions for SEQ ID NO: 1-217 are shown in Table 2 below.

Using eMatrix software package (Stanford University, Stanford, CA) (Wu et al., J. Comp. Biol., Vol. 6 pp. 219-235 (1999) herein incorporated by reference), all the sequences were examined to determine whether they had identifiable signature regions. Table 3 shows the signature region found in the indicated polypeptide sequences, the description of the signature, the eMatrix p-value(s) and the position(s) of the signature within the polypeptide sequence.

Using the pFam software program (Sonnhammer et al., Nucleic Acids Res., Vol. 26(1) pp. 320-322 (1998) herein incorporated by reference) all the polypeptide sequences were examined for domains with homology to certain peptide domains. Table 4 shows the name of the domain found, the description, the p-value and the pFam score for the identified domain within the sequence.

The nucleotide sequence within the sequences that codes for signal peptide sequences and their cleavage sites can be determine from using Neural Network SignalP V1.1 program (from Center for Biological Sequence Analysis, The Technical University of Denmark). The process for identifying prokaryotic and eukaryotic signal peptides and their cleavage sites are also disclosed by Henrik Nielson, Jacob Engelbrecht, Soren Brunak, and Gunnar von Heijne in the publication "Identification of prokaryotic and eukaryotic signal peptides and prediction of their cleavage sites" Protein Engineering, Vol. 10, no. 1, pp. 1-6 (1997), incorporated herein by reference. A maximum S score and a mean S score, as described in the Nielson et as reference, was obtained for the polypeptide sequences. Table 5 shows the position of the signal peptide in each of the polypeptides and the maximum score and mean score associated with that signal peptide.

### 5.3.2 EXAMPLE 4

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### **Novel Nucleic Acids**

Using PHRAP (Univ. of Washington) or CAP4 (Paracel), a full length gene cDNA sequence and its corresponding protein sequence were generated from the assemblage. Any frame shifts and incorrect stop codons were corrected by hand editing. During editing, the sequence was checked using FASTY and/or BLAST against Genbank (i.e., dbEST version 118, gb pri 118, UniGene version 118, Genpept release 118). Other computer programs which may have been used in the editing process were phredPhrap and Consed (University of Washington) and ed-ready, edext and gc-zip-2 (Hyseq, Inc.). The full-length nucleotide, including splice variants resulting from these procedures are shown in the Sequence Listing as SEQ ID NOS: 218-236.

Table 1 shows the various tissue sources of SEQ ID NO: 218-236.

The homology results for SEQ ID NO: 218-236 were obtained by a BLASTP version 2.0al 19MP-WashU search against Genpept release 120 and Geneseq October 12, 2000 release

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21 (Derwent), using BLAST algorithm. The nearest neighbor result showed the homologs for SEQ ID NO: 218-236 from Genpept. The translated amino acid sequences for which the nucleic acid sequence encodes are shown in the Sequence Listing. The homologues with identifiable functions for SEQ ID NO: 218-236 are shown in Table 2 below.

Using eMatrix software package (Stanford University, Stanford, CA) (Wu et al., J. Comp. Biol., Vol. 6 pp. 219-235 (1999) herein incorporated by reference), all the sequences were examined to determine whether they had identifiable signature regions. Table 3 shows the signature region found in the indicated polypeptide sequences, the description of the signature, the eMatrix p-value(s) and the position(s) of the signature within the polypeptide sequence.

Using the pFam software program (Sonnhammer et al., Nucleic Acids Res., Vol. 26(1) pp. 320-322 (1998) herein incorporated by reference) all the polypeptide sequences were examined for domains with homology to certain peptide domains. Table 4 shows the name of the domain found, the description, the p-value and the pFam score for the identified domain within the sequence.

The nucleotide sequence within the sequences that codes for signal peptide sequences and their cleavage sites can be determine from using Neural Network SignalP V1.1 program (from Center for Biological Sequence Analysis, The Technical University of Denmark). The process for identifying prokaryotic and eukaryotic signal peptides and their cleavage sites are also disclosed by Henrik Nielson, Jacob Engelbrecht, Soren Brunak, and Gunnar von Heijne in the publication "Identification of prokaryotic and eukaryotic signal peptides and prediction of their cleavage sites" Protein Engineering, Vol. 10, no. 1, pp. 1-6 (1997), incorporated herein by reference. A maximum S score and a mean S score, as described in the Nielson et as reference, was obtained for the polypeptide sequences. Table 5 shows the position of the signal peptide in each of the polypeptides and the maximum score and mean score associated with that signal peptide.

Table 6 is a correlation table of all of the sequences and the SEQ ID NOS.

### TABLE 1

Tissue Origin	RNA Source	Library Name	SEQ ID NOS:
adult brain	GIBCO	AB3001	3 15 19 74 88 174
			212-213 229
adult brain	GIBCO	ABD003	1-4 14 33 44 57 73-74
			78 88 108 145 148
			174 196 209-213 215
			218 235
adult brain	Clontech	ABR001	8 118 145 155 174
			192 208
adult brain	Clontech	ABR006	2 25 35-36 214 220
adult brain	Clontech	ABR008	1 4 13-14 16 25 33
			35-36 41-43 45 50 56
,			65 80 86 88 95 108
			110-112 118 129 141
			145 158-159 162 164
		1	169-171 173-174 189
			196 208-211 215 218-
			220 222-223 228
adult brain	Clontech	ABR011	211
adult brain	Invitrogen	ABR013	48 109 121 158-159
			199
adult brain	Invitrogen	ABT004	3-4 14 35-36 88 145
			174 196 210-211 222
		į.	224 228
cultured preadipocytes	Strategene	ADP001	2 6-8 13 69 73 193
			210 212-213 225 229
adrenal gland	Clontech	ADR002	3-4 7-8 12-14 21 33
			38 48 54 74 81 86-87
			145 158-159 163 208
, in the second			211-213 221 229 235
adult heart	GIBCO	AHR001	1-2 9 11 14-15 33 37
			39-41 61-62 73-75
			102 145-146 148 187
			196 210-213 218 222
			224-225 235
adult kidney	GIBCO	AKD001	1-4 8 10 12 14-15 33-
			34 37 39-40 43-48 54
			59 73-74 79-80 88
			107-108 118 121 138
			145 159 163 169-171
			173-174 186 196 209-
adult leida as	T	A 7/7000	215 224 229 235
adult kidney	Invitrogen	AKT002	1 8 12 14 35-36 47-48
			86 118 130 148 158-
			159 196 210 222-223
adult lung	GIBCO	AT C001	225 235
adult imig	GIBCO	ALG001	12 16 37 56 73 88 96-
			99 106 114 145 148
			155 164 216-217 228- 229
	L .		229

Tissue Origin	RNA Source	Library Name	SEQ ID NOS:
lymph node	Clontech	ALN001	12 41 47-48 94 96-99
			107-109 121 145 158-
			159 172 191
young liver	GIBCO	ALV001	3 8 14 39-40 48 58 64
,			66 86 104 108 140
			145 158-160 169-171
			174 189 211-214 216-
			217 229 235
adult liver	Invitrogen	ALV002	4 16 37 39-40 66 73
			86 105 145 169-171
			173 189 192 194-196
	į		209 211 214 222 224
		· ·	228
adult liver	Clontech	ALV003	214
adult ovary	Invitrogen	AOV001	1 3-4 7 11-16 18 20
udun ovary	111.111.08012		34-37 39-40 42-45 48
		ļ	57-59 70-74 76 78 80
		•	88 96-99 102 108 118
		1	140-141 145-148 155
			157-160 162-164
			172-175 182 187 196
			209-213 220-222 225
		ļ	228-229 235
adult placenta	Invitrogen	APL001	14 45 222
placenta	Invitrogen	APL002	55 138
adult spleen	GIBCO	ASP001	2-4 8 11-12 33 39-40
addit spissin			44 47-48 74 80 96-99
			107-110 121 145 155
•			158-159 164 172 174
		•	191 211-213 216-217
			222 229 235
testis	GIBCO	ATS001	2 35-37 39-40 175
			196 212-213 235
adult bladder	Invitrogen	BLD001	5 7-8 14 73 138 141
			159 196 235
bone marrow	Clontech	BMD001	2 4 7 12 19 39-40 47-
			48 57 63 74 80 94 96-
			99 103 107-108 118
			121 140 145 149 156
			158-160 169-172 186
			191 210 212-213 215
			229
bone marrow	Clontech	BMD002	1 4 12 14 33 35-36 41
			44-45 47-48 74 88
			96-99 107-108 110
		1	118 158-160 173 190-
			191 209 212-213 223
bone marrow	Clontech	BMD004	7 48 96-99 158-159
			212-213
adult colon	Invitrogen	CLN001	2 11-12 80 96-99 140
	1	·	191

Tissue Origin	RNA Source	Library Name SEQ ID NOS:		
adult cervix	BioChain	CVX001	1-2 12 14-15 26 33	
			35-36 39 42-43 47 54	
			73 80 88 95 107 129-	
			137 150 196 212-213	
			220-221 224 227-229	
			235	
endothelial cells	Strategene	EDT001	2 4 8 14 33-36 39-40	
			42-43 56 67-69 73-74	
			80 88 95 108-109 116	
			121 132 140 145 163	
			173 209 211-213 223	
			225 228-229	
Genomic clones from	Genomic DNA from	EPM001	206-207	
the short arm of	Genetic Research			
chromosome 8	·			
Genomic clones from	Genomic DNA from	EPM003	207	
the short arm of	Genetic Research		İ	
chromosome 8		1		
Genomic clones from	Genomic DNA from	EPM004	207	
the short arm of	Genetic Research		!	
chromosome 8				
fetal brain	Clontech	FBR006	2 4 8 25 41 74 111-	
Total Oralli	O.O.I.LOOII		112 141 143 162 187	
			196 210-213 215-217	
			219-220 222-223 228	
fetal brain	Invitrogen	FBT002	4 14 16 18 35-36 65	
Total orall	Invitro Bon		74 78 80 111-112 139	
	1		157 173-174 196 209-	
			211 220-221	
fetal kidney	Clontech	FKD001	7 33 46 65 108 211-	
10000			213	
fetal kidney	Clontech	FKD002	80 212-213	
fetal lung	Clontech	FLG001	108 118 155	
fetal lung	Invitrogen	FLG003	3 39-40 145 211 222	
fetal liver-spleen	Columbia University	FLS001	1-4 7-8 10 14-17 22	
Total invol opioon	Columnia of the colors,		28 33-40 42-44 48	
			52-53 60 66 68 74 88	
			96-99 102 108 110-	
			112 117 136 138 140	
			143 145 148 154 158-	
•			159 163 169-172 174	
*			181 191 196 201 209-	
			217 220 222-224 228-	
			229 231 235	
fetal liver-spleen	Columbia University	FLS002	1-2 7-8 11 14-15 27-	
Trust III opioon			28 33-37 39-40 44 53	
			60 68 73-75 80 86 91	
			95 108 110 115 122-	
			128 138 140 143 145	
			154-155 164 169-172	
			175 182-186 190 196	
	_L		17.5 102 100 170 170	

Tissue Origin	RNA Source	Library Name	SEQ ID NOS:	
			200-205 209 212-214	
			216-217 220 222-225	
			230-231 235	
fetal liver-spleen	Columbia University	FLS003	214 223-224	
fetal liver	Invitrogen	FLV001	3 8 41 66 73-74 80 88	
			95 108 110 145 148	
			154 169-171 173 196	
			211 214	
fetal liver	Clontech	FLV004	7	
fetal muscle	Invitrogen	FMS001	7 11 14 37 43 79 139	
			196 211 224-225 228	
fetal muscle	Invitrogen	FMS002	7	
fetal skin	Invitrogen	FSK001	7-8 14 33 35-37 39 74	
			88 108 142 162 172-	
			175 196 210-213 215	
			220 222	
fetal skin	Invitrogen	FSK002	7 196 235	
fetal spleen	BioChain	FSP001	8 96-99	
umbilical cord	BioChain	FUC001	7 13-14 20 37 56 102	
			108 113 145 148 160	
	ì		176-180 199 209 212-	
			213 222	
fetal brain	GIBCO	HFB001	2 13-15 37 42-43 57	
201112			73 88 108 111-112	
			118 129 163 174 192	
			196 199 208-213 215	
			224-225 229 235	
macrophage	Invitrogen	HMP001	44	
infant brain	Columbia University	IB2002	1 8 14 16 31 37 57 64	
			77 80 88 108 111-112	
			151 162 174 192 196	
			210-213 215 223 225	
			229	
infant brain	Columbia University	IB2003	7 31 57 88 94 148	
			162 174 196-198 210-	
			213 215 224-225	
infant brain	infant brain Columbia University		8	
infant brain	Columbia University	IBS001	31 42-43 111-112 196	
			211	
Lung, fibroblast	Lung, fibroblast Strategene		4 73 174 196 199 222	
lung tumor	Invitrogen	LGT002	2-3 5 7-9 11-12 14 22	
-			24 37 39-40 42-44	
			47-48 57 73 86 102	
			106 109-110 121 140	
			145 148 155 158-160	
			162 164-166 169-171	
			186 196 209-213 216-	
			218 220 222-223 228	
lymphocytes	ATCC	LPC001	13 30 39-40 42-44	
-ypooy.co			119 153 158-159 186-	
	-		188 209 211 222 226	

Tissue Origin	RNA Source	Library Name	SEQ ID NOS:
			232-234 236
leukocyte	GIBCO	LUC001	4-5 11 13 16 29-30 32
•			34 39-41 44 47-51 57
			74 80 88 96-99 107-
			110 116 121 129 145
			148 152-155 158-160
			163-164 172 186 190-
			191 196 210-213 216-
·			217 219 229 235
leukocyte	Clontech	LUC003	109 121 145 155 160
	01	NACT OOA	212-213 235
melanoma from cell line ATCC #CRL	Clontech	MEL004	2 4 22 33 140 192 199 211-213 222 228
1424			
mammary gland	Invitrogen	MMG001	1-2 4 7-8 12 14 22
			35-37 39-40 42-44
			47-48 51 59 73-74 80
			88 96-99 107 109 116 121 138 145 148 162
			167-174 191-192 196
	1		209-213 215 218 221-
			222 224-225 228
induced neuron cells	Strategene	NTD001	163 192 209 224
retinoid acid induced	Strategene	NTR001	211-213 223
neuronal cells			
neuronal cells	Strategene	NTU001	2 8 14 39-40 209 211
<u> </u>			215 224
placenta	Clontech	PLA003	145
prostate	Clontech	PRT001	4 8 14 211 218 229 235
rectum	Invitrogen	REC001	12 14 48 73 96-99
			143 158-159 169-171
			174 196 211 224-225
salivary gland	Clontech	SAL001	4 12 37 47-48 70 74
			107 109 114 121 144
			158-159 174 196 212-
			213 220
small intestine	Clontech	SIN001	12 39-40 47 74 82-83
			89-90 96-99 107 117-
•			118 173 191 222 224
	01	010 ( 04	229 235
skeletal muscle	Cloatech	SKMs04	88
spinal cord	Clontech	SPC001	1 4 14 27 88 91-92 108 119-120 145 174
			212-213 220 235
adult spleen	Clontech	SPLc01	158-159 219 229 235
stomach	Clontech	STO001	4 37 48 93-95 115
		101001	T J   TO JJ-JJ       J
Storitation	Cionicon		138 159 216-217
		THA002	138 159 216-217 37 94 125 139 174
thalamus thymus	Clontech Clontech	THA002 THM001	138 159 216-217 37 94 125 139 174 8 12 22 25 39-40 84

Tissue Origin	RNA Source	Library Name	SEQ ID NOS:	
			191 212-213 222	
thymus	Clontech	THMc02	4-5 14 33 42-44 48 50	
,			57 59 73-74 78 96-99	
		•	109 121 141 145 148	
		Ī	155-162 172 187 191	
			210 212-213 219 223	
			228	
thyroid gland	Clontech	THR001	4 8-9 14 23 37 39-40	
unjusta giana			48 54 57 74 86 100-	
		•	101 107 118 140 159	
		į	169-171 196 209-211	
		1	225 229 235	
trachea	Clontech	TRC001	11 37 48 85 95-99	
			114 118 159 172 191	
			212-213	
uterus	Clontech	UTR001	8 102-103 227 235	

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TABLE 2

SEQ	ACCESSION	SPECIES	DESCRIPTION	SMITH-	%
ID `	NUMBER		·	WATERMAN	IDENTITY
NO:				SCORE	
1	AJ222644	Arabidopsis	asparaginyl-tRNA	659	50
		thaliana	synthetase		
2	Y57899	Homo	Human transmembrane	2044	99
	-	sapiens	protein HTMPN-23.		
3	Y20291	Homo	Human apolipoprotein E	1080	91
		sapiens	wild type protein		
<del></del> -	-	\ <u></u>	fragment 1.		100
4	D42138	Homo	PIG-B	3001	100
	17140145	sapiens		1450	70
5	AF148145	Mus	putative thymic stromal	1459	78
	1110000	musculus	co-transporter TSCOT	1100	100
6	X68657	Rattus	granzyme-like protein II	1138	89
	774616	norvegicus	11.10	0016	100
7	Z74615	Homo	prepro-alpha1(I) collagen	8216	99
<del></del>	D13623	sapiens	24	1482	94
9		Rattus sp.	p34 protein	1	99
9	Y94263	Homo	Human phospholipid	1185	99
		sapiens	binding protein 2, PLBP2.		
11	Y29939	Homo	Human retinol	1663	100
11	1 47737	sapiens	dehydrogenase type II	1003	100
		Sapiciis	homologue.		
12	Y14738	Homo	immunoglobulin lambda	1144	91
124	111750	sapiens	light chain		
13	AF156549	Mus	putative E1-E2 ATPase	4825	79
	111 130317	musculus	patter of the second	1023	' '
14	Y00815	Homo	put. LAR preprotein (AA	9947	99
		sapiens	-16 to 1881)		
19	Y11584	Homo	Human 5' EST secreted	192	100
		sapiens	protein SEQ ID NO:236.		
25	Y70210	Homo	Human TANGO 130	991	95
		sapiens	protein.		
31	D26093	Gallus	VMO-I	463	52
		gallus			
32	AE000658	Homo	TCRAV4S1	558	100
		sapiens			
33	W64542	Homo	Human stomach cancer	483	100
		sapiens	cell clone HP10071		
			protein.		
34	Y87342	Homo	Human signal peptide	690	100
	·	sapiens	containing protein HSPP-		
			119 SEQ ID NO:119.		
35	AL049795	Homo	dJ622L5.8.1 (novel	399	96
		sapiens	protein (isoform 1))		
36	AL049795	Homo	dJ622L5.8.1 (novel	458	100
		sapiens	protein (isoform 1))		

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SEQ	ACCESSION	SPECIES	DESCRIPTION	SMITH-	% IDENTITY
ID NO:	NUMBER			WATERMAN SCORE	IDENTITY
37	Y44273	Homo	Human Metabotropic	2458	99
		sapiens	Glutamate Receptor-like		
			protein, MGRcm.		
39	AF111713	Homo	junctional adhesion	1544	100
		sapiens	molecule		
40	AF154005	Homo	junction adhesion	1333	100
		sapiens	molecule		
41	Y35960	Homo	Extended human secreted	500	98
		sapiens	protein sequence, SEQ ID NO. 209.		
42	AF247174	synthetic	RP6-alkaline	140	36
		construct	phosphatase hybrid		
			protein		1
43	AF179415	Dendroides	antifreeze protein 11	132	30
		canadensis	•		
44	W01049	Homo	Product of 200 gene	1580	99
		sapiens	differentially expressed		1
		_	in T helper cells.		<u>.</u>
45	AL121929	Homo	bA416N2.2 (similar to	5039	100
		sapiens	murine FISH (an SH3		1
			and PX domain-		
	}		containing protein, and		
			Src substrate))		
47	X57816	Homo	immunoglobulin lambda	1212	100
		sapiens	light chain		
48	W88464	Homo	Monoclonal antibody	2162	86
		sapiens	4B5 heavy chain variable		
			region.		
50	AE003523	Drosophila	CG7510 gene product	280	54
		melanogaste			
		r			
54	AF231128	Danio rerio	Dap1b	165	42
55	AB047612	Macaca	hypothetical protein	330	98
		fascicularis	77 77 77 77	1070	1
56	Y41701	Homo	Human PRO708 protein	1070	99
	1	sapiens	sequence.	104	1
65	Y73351	Homo	HTRM clone 1484257	104	39
	1.5100555	sapiens	protein sequence.	0066	100
66	AF188285	Homo	bone morphogenetic	2266	100
	1 . 5000000	sapiens	protein 9	1000	<del> </del>
73	AE002038	Deinococcu	ribosomal protein L20	202	41
		S			
	10160000	radiodurans	2010	1252	100
74	AF157321	Homo	30 kDa protein	1252	99
	1.0004500	sapiens		100	103
79	AC004522	Homo	gap junction protein;	482	93
		sapiens	similar to P36383		
			(PID:g544117)		

SEQ	ACCESSION	SPECIES	DESCRIPTION	SMITH-	%
ID	NUMBER	,		WATERMAN	IDENTITY
NO:	1.7.055015		PODO	SCORE	100
80	AL355715	Homo sapiens	PCD9	2075	100
86	Y76140	Homo	Human secreted protein	692	97
		sapiens	encoded by gene 17.		
88	AL020993	Homo sapiens	dJ5O6.2 (novel protein similar to C. elegans F40E10.6 (isoform 1))	1545	100
91	AC004896	Homo sapiens	similar to contactin associated protein; similar to U87223 (PID:g1857708)	157	58
92	G00517	Homo sapiens	Human secreted protein, SEQ ID NO: 4598.	124	54
94	Y27593	Homo sapiens	Human secreted protein encoded by gene No. 27.	248	58
95	Y92507	Homo sapiens	Human OXRE-4 with identity to 3-oxo-5-alphasteroid dehydrogenase.	1715	100
96	AJ006112	Homo sapiens	anti-(ED-B) scFV	1238	100
97	AF174012	Homo sapiens	immunoglobulin heavy chain variable region precursor	692	91
98	AJ006111	Homo sapiens	anti-(ED-B) scFV	1166	93
99	AJ006112	Homo sapiens	anti-(ED-B) scFV	1046	84
102	AF137378	Homo sapiens	integrin alpha 11 subunit precursor	6224	99
106	W62068	Homo sapiens	Human lung tissue gene LU103 protein.	333	97
107	X57802	Homo sapiens	immunoglobulin lambda light chain	1160	95
108	Y41697	Homo sapiens	Human PRO700 protein sequence.	1441	100
109	M12886	Homo sapiens	T-cell receptor beta chain	1590	98
110	U71383	Homo sapiens	OB binding protein-2	2913	99
111	AB035356	Homo sapiens	neurexin I-alpha protein	4390	76
112	L14851	Rattus norvegicus	neurexin III-alpha	5614	97
114	X60660	Rattus rattus	potential ligand-binding protein	382	27
116	L03785	Homo sapiens	myosin regulatory light chain	873	100
118	Y58637	Homo	Protein regulating gene	246	30

SEQ ID NO:	ACCESSION NUMBER	SPECIES	DESCRIPTION	SMITH- WATERMAN SCORE	% IDENTITY
		sapiens	expression PRGE-30.		
121	M12886	Homo sapiens	T-cell receptor beta chain	1536	96
129	AL031985	Homo sapiens	dJ228H13.3 (zinc finger protein)	2364	100
138	Y59664	Homo sapiens	Secreted protein 108- 004-5-0-E8-FL.	973	98
139	AF139980	Homo sapiens	LW-1	2275	100 .
140	Y28279	Homo sapiens	Human G-protein coupled receptor GRIR-1.	742	100
141	AF287892	Homo sapiens	sialic acid binding immunoglobulin-like lectin 8 long splice variant	1320	96
145	X00699	Homo sapiens	precursor	1400	98
146	AB036849	Ciona intestinalis	fibrinogen-like protein	184	40
148	W78169	Homo sapiens	Human secreted protein encoded by gene 44 clone HETFJ05.	2114	98
154	AF109683	Homo sapiens	leukocyte-associated Ig- like receptor 1b	174	25
155	W99070	Homo sapiens	Human PIGR-1.	434	53
158	AF184764	Homo sapiens	IgG1 heavy chain	939	79
159	Y14737	Homo sapiens	immunoglobulin lambda heavy chain	2559	100
160	AF043171	Homo sapiens	T cell receptor alpha chain	1479	100
162	AB000199	Rattus norvegicus	CCA2 protein	822	87
163	AF186273	Homo sapiens	leucine-rich repeats containing F-box protein FBL3	251	32
164	AF227924	Homo sapiens	sialic acid-binding lectin Siglec-9	2459	99
167	AF098807	Homo sapiens	lipoma HMGIC fusion	713	63
168	AF098807	Homo sapiens	lipoma HMGIC fusion	443	57
169	Y66706	Homo sapiens	Membrane-bound protein PRO1129.	2786	99
170	Y66706	Homo sapiens	Membrane-bound protein PRO1129.	1733	98

SEQ	ACCESSION	SPECIES	DESCRIPTION	SMITH-	%
ID	NUMBER			WATERMAN	IDENTITY
NO:				SCORE	
171	Y66706	Homo sapiens	Membrane-bound protein PRO1129.	1058	93
173	W67898	Homo	Human secreted protein	838	95
		sapiens	encoded by gene 16 clone HE9DG49.		
174	Y06115	Homo sapiens	Human organic cation transporter OCT-3.	1876	100
182	G02872	Homo sapiens	Human secreted protein, SEQ ID NO: 6953.	262	59
186	AE003652	Drosophila melanogaste r	CG17996 gene product	115	66
187	AF166350	Homo sapiens	ST7 protein	4716	100
189	AF202889	Homo sapiens	regeneration associated protein 3	1864	100
191	AF090418	Homo sapiens	scFV anitbody V-region	1010	85
192	AJ010231	Homo sapiens	RET finger protein-like 2	1522	100
193	U65579	Homo sapiens	mitochondrial NADH dehydrogenase- ubiquinone Fe-S protein 8, 23 kDa subunit precursor	981	89
196	AF161444	Homo sapiens	HSPC326	1467	96
199	D26179	Rattus norvegicus	V-1 protein	479	100
208	L22031	Glycine max	hydroxyproline-rich glycoprotein	99	34
209	AF201931	Homo sapiens	DC1	1662	99
210	W74882	Homo sapiens	Human secreted protein encoded by gene 154 clone HE6FL83.	480	100
211	U53925	Mus musculus	transcription factor C1 (HCF)	297	31
212	AJ251914	Sus scrofa	putative RNA helicase	2199	100
213	AJ251914	Sus scrofa	putative RNA helicase	1571	100
214	X04494	Homo sapiens	precursor polypeptide	1903	100
215	Y66699	Homo sapiens	Membrane-bound protein PRO1108.		100
216	AJ130710	Homo sapiens	QA79 membrane protein, allelic variant airm-1b	2473	100
217	AJ130711	Homo sapiens	QA79 membrane protein, splice product airm-2	1969	100

SEQ	ACCESSION	SPECIES	DESCRIPTION	SMITH-	%
ID	NUMBER			WATERMAN	IDENTITY
NO:				SCORE	<u> </u>
218	AF233523	Homo	beta V spectrin	18612	99
		sapiens			<u> </u>
219	AF127481	Homo	non-ocogenic Rho	743	36
		sapiens	GTPase-specific GTP		
			exchange factor		
220	Y71066	Homo	Human membrane	2378	99
		sapiens	transport protein, MTRP-		
			11		
221	AF132730	Homo	unknown	1899	100
	·	sapiens			
223	W54097	Homo	Homo sapiens B223	1834	99
		sapiens	sequence.		
224	Y99449	Homo	Human PRO1760	1017	100
		sapiens	(UNQ833) amino acid		
			sequence SEQ ID		
			NO:376.		
225	Y92368	Homo	G protein-coupled	2293	100
		sapiens	receptor protein 8.		
227	Y99436	Homo	Human PRO1474	464	100
		sapiens	(UNQ745) amino acid		
			sequence SEQ ID		
			NO:334.		
228	AK024825	Homo	unnamed protein product	1375	99
	·	sapiens			100
229	G03186	Homo	Human secreted protein,	307	96
		sapiens	SEQ ID NO: 7267.		<del> </del>
235	AB025606	Arabidopsis	contains similarity to	753	46
		thaliana	GTPase activating		1
			protein~gene_id:F6N7.7	<u> </u>	

## TABLE 3

SEQ ID	ACCESSION	DESCRIPTION	RESULTS*
NO:	NO.		
1	PF00152	tRNA synthetases class II.	PF00152D 21.30 8.364e-28 422-461
			PF00152C 28.03 9.250e-21 220-257
			PF00152B 15.67 2.658e-13 159-184
			PF00152A 19.68 5.714e-11 44-67
2	PR00237	RHODOPSIN-LIKE	PR00237F 13.57 5.263e-09 158-183
		GPCR SUPERFAMILY	
		SIGNATURE	
3	PD02807	APOLIPOPROTEIN E	PD02807B 8.27 1.000e-40 64-103
		PRECURSOR APO-E	PD02807C 8.91 1.000e-40 139-188
		GLYCOPROTEIN PLAS.	PD02807D 7.99 1.000e-40 188-238
			PD02807A 12.43 6.143e-25 27-48
			PD02807C 8.91 5.645e-09 95-144
5	PD01572	PHOTOSYSTEM II	PD01572 8.77 6.917e-09 213-243
		REACTION CENTRE T	·
		PROTEIN PHOTOS.	27.00104.11.06.0105.15.50.65
6	BL00134	Serine proteases, trypsin	BL00134A 11.96 2.125e-15 50-67
		family, histidine proteins.	BL00134B 15.99 7.618e-13 195-219
7	DM01418	352 FIBRILLAR	DM01418A 20.83 1.000e-40 1252-1300
		COLLAGEN	DM01418B 22.51 1.000e-40 1351-1393
		CARBOXYL-	DM01418C 20.48 5.500e-40 1422-1464
<u> </u>	DI 00224	TERMINAL.	BL00224B 16.94 1.082e-09 166-219
8	BL00224	Clathrin light chain	BL00224B 10.94 1.082e-09 100-219
9	BL01220	proteins.  Phosphatidylethanolamine-	BL01220B 16.65 6.774e-23 85-126
9	BLUIZZU	binding protein family	BL01220B 16.63 6.774e-23 83-126 BL01220C 14.75 5.857e-17 130-158
		proteins.	BL01220C 14.73 3.8376-17 130-138
11	PR00081	GLUCOSE/RIBITOL	PR00081C 15.13 5.846e-11 151-168
11	FROODS	DEHYDROGENASE	1 K00081C 13.13 3.840E-11 131-108
		FAMILY SIGNATURE	
12	BL00290	Immunoglobulins and	BL00290A 20.89 1.529e-14 159-182
12	BEOOZSO	major histocompatibility	BL00290B 13.17 9.000e-12 219-237
		complex proteins.	
13	PR00121	SODIUM/POTASSIUM-	PR00121D 16.72 2.694e-12 113-135
		TRANSPORTING	
ļ		ATPASE SIGNATURE	
14	PR00700	PROTEIN TYROSINE	PR00700B 16.80 1.500e-24 1420-1441
		PHOSPHATASE	PR00700D 12.47 4.214e-22 1543-1562
		SIGNATURE	PR00700B 16.80 4.240e-21 1709-1730
			PR00700D 12.47 7.158e-20 1834-1853
			PR00700C 13.17 5.800e-18 1504-1522
		·	PR00700C 13.17 7.353e-17 1793-1811
1			PR00700E 17.57 4.000e-14 1865-1881
-			PR00700F 11.18 7.353e-13 1590-1601
			PR00700F 11.18 1.429e-12 1881-1892
			PR00700E 17.57 5.304e-12 1574-1590
			PR00700A 6.96 8.714e-11 1404-1412
31	PD02382	RECEPTOR CHAIN	PD02382B 4.60 7.000e-09 105-112
L		PRECURSOR	

SEQ ID NO:	ACCESSION NO.	DESCRIPTION	RESULTS*
		TRANSME.	
37	BL00979	G-protein coupled receptors family 3 proteins.	BL00979L 20.63 2.485e-09 150-191
39	DM00179	w KINASE ALPHA ADHESION T-CELL.	DM00179 13.97 1.000e-11 102-112
40	DM00179	w KINASE ALPHA ADHESION T-CELL.	DM00179 13.97 1.000e-11 62-72
45	BL50002	Src homology 3 (SH3) domain proteins profile.	BL50002B 15.18 3.000e-09 953-967
47	BL00290	Immunoglobulins and major histocompatibility complex proteins.	BL00290A 20.89 1.529e-14 150-173 BL00290B 13.17 9.000e-12 210-228
48	DM00031	IMMUNOGLOBULIN V REGION.	DM00031A 16.80 9.775e-36 20-68 DM00031B 15.41 7.600e-21 84-118 DM00031C 12.79 8.929e-10 131-142
56	BL00523	Sulfatases proteins.	BL00523C 12.64 4.000e-13 314-325 BL00523A 13.36 7.300e-13 222-239 BL00523B 8.64 6.114e-11 268-280
65	BL00028	Zinc finger, C2H2 type, domain proteins.	BL00028 16.07 4.115e-11 204-221
66	BL00250	TGF-beta family proteins.	BL00250A 21.24 3.000e-24 327-363 BL00250B 27.37 1.000e-15 393-429
73	PR00062	RIBOSOMAL PROTEIN L20 SIGNATURE	PR00062C 16.68 7.245e-15 82-109 PR00062B 16.66 2.658e-11 49-79
79	BL00407	Connexins proteins.	BL00407E 22.17 8.820e-23 169-214 BL00407B 14.23 6.311e-20 39-70 BL00407C 14.61 1.164e-18 70-98 BL00407A 18.57 6.250e-13 2-39 BL00407D 17.61 5.790e-12 131-161
96	BL00290	Immunoglobulins and major histocompatibility complex proteins.	BL00290A 20.89 3.520e-10 281-304
97	DM00031	IMMUNOGLOBULIN V REGION.	DM00031A 16.80 1.000e-40 20-68 DM00031B 15.41 1.000e-36 84-118 DM00031C 12.79 1.600e-15 127-138
98	BL00290	Immunoglobulins and major histocompatibility complex proteins.	BL00290A 20.89 3.520e-10 286-309
99	BL00290	Immunoglobulins and major histocompatibility complex proteins.	BL00290B 13.17 4.000e-12 341-359 BL00290A 20.89 3.520e-10 280-303
102	PR00453	VON WILLEBRAND FACTOR TYPE A DOMAIN SIGNATURE	PR00453A 12.79 9.719e-13 163-181 PR00453B 14.65 1.818e-12 200-215 PR00453C 12.26 3.769e-10 265-274
107	BL00290	Immunoglobulins and major histocompatibility complex proteins.	BL00290A 20.89 1.563e-15 151-174 BL00290B 13.17 9.000e-12 211-229
108	BL00194	Thioredoxin family proteins.	BL00194 12.16 2.565e-13 46-59 BL00194 12.16 3.348e-13 179-192

SEQ ID	ACCESSION	DESCRIPTION	RESULTS*
NO:	NO.	DESCRIPTION	
109	BL00290	Immunoglobulins and	BL00290A 20.89 8.200e-12 160-183
		major histocompatibility	
		complex proteins.	
111	BL00964	Syndecans proteins.	BL00964B 12.05 2.604e-10 981-1024
112	BL00964	Syndecans proteins.	BL00964B 12.05 2.604e-10 1011-1054
114	BL00400	LBP / BPI / CETP family	BL00400D 23.26 7.222e-12 251-288
		proteins.	•
116	BL00018	EF-hand calcium-binding	BL00018 7.41 1.391e-09 43-56
		domain proteins.	
121	BL00290	Immunoglobulins and	BL00290A 20.89 8.200e-12 159-182
		major histocompatibility	
		complex proteins.	
129	BL00028	Zinc finger, C2H2 type,	BL00028 16.07 8.875e-15 347-364
		domain proteins.	BL00028 16.07 6.824e-14 207-224
			BL00028 16.07 7.353e-14 403-420
			BL00028 16.07 8.650e-13 235-252
			BL00028 16.07 8.435e-12 319-336
			BL00028 16.07 3.077e-11 291-308 :
			BL00028 16.07 3.769e-11 263-280
		İ	BL00028 16.07 5.154e-11 179-196
			BL00028 16.07 4.000e-10 375-392
132	PR00836	SOMATOTROPIN	PR00836B 16.59 8.347e-09 3-22
		HORMONE FAMILY	
		SIGNATURE	77 200 5 60 14 15 7 200 10 15 2 16 6
139	PR00056	HEAT SHOCK FACTOR	PR00056C 14.47 7.823e-12 153-166
		(HSF) DOMAIN	
	77700045	SIGNATURE	PR00245A 18.03 7.300e-19 82-104
140	PR00245	OLFACTORY RECEPTOR SIGNATURE	PR00243A 18.03 7.300e-19 82-104
145	DE00000		PF00969B 9.97 1.000e-40 58-94
145	PF00969	Class II histocompatibility	PF00969C 27.72 1.000e-40 97-147
		antigen, beta domain proteins.	PF00969E 11.49 1.000e-39 212-247
		proteins.	PF00969A 22.07 3.520e-38 12-55
			PF00969D 14.02 4.789e-36 154-184
146	BL00514	Fibrinogen beta and	BL00514C 17.41 2.579e-24 181-218
140	BL00314	gamma chains C-terminal	BL00514G 15.98 9.111e-12 262-292
		domain proteins.	550001101000000000000000000000000000000
155	DM01688	2 POLY-IG RECEPTOR.	DM01688B 15.06 3.628e-09 82-130
158	DM00031	IMMUNOGLOBULIN V	DM00031A 16.80 1.000e-40 20-68
1.50	21.100031	REGION.	DM00031B 15.41 5.865e-25 86-120
			DM00031C 12.79 4.429e-10 129-140
159	DM00031	IMMUNOGLOBULIN V	DM00031A 16.80 1.000e-40 20-68
1	2	REGION.	DM00031B 15.41 1.000e-40 84-118
			DM00031C 12.79 1.600e-15 134-145
160	DM00031	IMMUNOGLOBULIN V	DM00031B 15.41 6.294e-12 85-119
		REGION.	
162	PF01073	3-beta hydroxysteriod	PF01073A 18.01 9.206e-22 140-193
	_	dehydrogenase/isomerase	PF01073B 12.26 6.831e-19 222-267
		family.	PF01073C 10.62 2.645e-17 322-370
169	BL00086	Cytochrome P450 cysteine	BL00086 20.87 3.813e-24 480-512

SEQ ID NO:	ACCESSION NO.	DESCRIPTION	RESULTS*
		heme-iron ligand proteins.	
170	BL00086	Cytochrome P450 cysteine	BL00086 20.87 3.813e-24 502-534
170	BECCCC	heme-iron ligand proteins.	
171	BL00086	Cytochrome P450 cysteine	BL00086 20.87 3.813e-24 363-395
171	DECOOR	heme-iron ligand proteins.	
173	BL00453	FKBP-type peptidyl-prolyl	BL00453B 23.86 3.000e-20 87-121
173	BL00433	cis-trans isomerase	BL00453A 15.57 9.379e-10 63-78
		proteins.	BB00 13311 15.57 315 736 15 15 15
174	BL00216	Sugar transport proteins.	BL00216B 27.64 4.900e-10 240-290
174	1	LDL-receptor class A	BL01209 9.31 5.500e-11 470-483
187	BL01209		BL01209 9.31 3.300c-11 470-403 BL01209 9.31 2.212e-10 395-408
		(LDLRA) domain proteins.	BL01209 9.31 2.2126-10 393-408 BL01209 9.31 6.365e-10 433-446
			BL01209 9.31 8.962e-10 239-252
189	PD01733	APOLIPOPROTEIN	PD01733B 20.44 6.600e-14 109-164
		PLASMA LIPID	
	·	TRANSPORT H.	
190	PR00237	RHODOPSIN-LIKE	PR00237E 13.03 8.412e-09 15-39
		GPCR SUPERFAMILY	
		SIGNATURE	
191	DM00031	IMMUNOGLOBULIN V	DM00031A 16.80 1.000e-40 61-109
		REGION.	DM00031B 15.41 1.000e-40 125-159
			DM00031C 12.79 1.600e-15 174-185
			DM00031B 15.41 9.544e-09 245-279
192	PF00622	Domain in SPla and the	PF00622B 21.00 8.250e-11 161-183
1,72	11000=	RYanodine Receptor.	
193	BL00198	4Fe-4S ferredoxins, iron-	BL00198 10.43 5.263e-12 152-164
'	BECCISO	sulfur binding region	BL00198 10.43 1.346e-10 113-125
		proteins.	
199	PF00023	Ank repeat proteins.	PF00023A 16.03 8.000e-12 90-106
208	BL00127	Pancreatic ribonuclease	BL00127C 31.49 7.288e-09 33-77
208	BL00127	family proteins.	BB001276 31.15 7.2000 05 05 77
210	BL01310	ATP1G1 / PLM / MAT8	BL01310 14.74 2.432e-29 71-107
210	Proisin	family proteins.	BE01510 14.74 2.1520 25 71 107
010	DI 00020		BL00039D 21.67 5.000e-26 340-386
212	BL00039	DEAD-box subfamily	BL00039D 21.07 5.000c-20 540-560
		ATP-dependent helicases	BL00039R 19.19 3.681e-11 104-130
	7,0000	proteins.	
213	BL00039	DEAD-box subfamily	BL00039D 21.67 5.000e-26 314-360 BL00039A 18.44 6.114e-17 64-103
		ATP-dependent helicases	
		proteins.	BL00039B 19.19 3.681e-11 104-130
214	BL00280	Pancreatic trypsin inhibitor	BL00280 24.61 6.727e-38 238-282
		(Kunitz) family proteins.	BL00280 24.61 1.514e-30 294-338
216	PF00064	Neuraminidases.	PF00064D 17.65 8.830e-09 11-50
217	PF00064	Neuraminidases.	PF00064D 17.65 8.830e-09 11-50
218	BL00019	Actinin-type actin-binding	BL00019D 15.33 7.585e-21 196-226
		domain proteins.	BL00019C 14.66 9.143e-20 128-164
			BL00019A 12.56 5.408e-12 56-67
			BL00019B 13.34 9.795e-12 83-106
219	PR00194	TROPOMYOSIN	PR00194D 9.57 1.240e-10 391-415
~ . ′		SIGNATURE	
L			

SEQ ID	ACCESSION	DESCRIPTION	RESULTS*
NO:	NO.		
220	BL00594	Aromatic amino acids permeases proteins.	BL00594A 16.75 4.743e-09 56-100
222	BL00415	Synapsins proteins.	BL00415N 4.29 8.695e-10 335-379
223	PR00217	43 KD POSTSYNAPTIC PROTEIN SIGNATURE	PR00217C 10.91 7.725e-09 302-318
225	PD02918	AMINOGLYCOSIDE N3'- ACETYLTRANSFERASE III.	PD02918A 18.79 3.621e-09 345-385
227	BL00282	Kazal serine protease inhibitors family proteins.	BL00282 16.88 4.717e-18 45-68
235	PR00356	TYPE II ANTIFREEZE PROTEIN SIGNATURE	PR00356G 10.80 8.644e-09 536-550

<sup>\*</sup> results include in order: accession number subtype, raw score; p-value; position of signature in amino acid sequence.

TABLE 4

EQ	PFAM NAME	DESCRIPTION	p-value	PFAM SCORE
D				SCORE
10:		The state of the s	1.1e-84	294.8
	tRNA-synt_2	tRNA synthetases class II (D, K and N)		
	Apolipoprotein	Apolipoprotein A1/A4/E family	7.3e-91	315.3
	trypsin	Trypsin	2.9e-59	189.2
,	Collagen	Collagen triple helix repeat (20 copies)	4.1e-290	977.2
	LRR	Leucine Rich Repeat	2.9e-13	57.5
)	PBP	Phosphatidylethanolamine-binding protein	1.4e-17	71.9
1	adh_short	short chain dehydrogenase	7e-43	155.9
12	ig	Immunoglobulin domain	2.1e-14	51.4
14	Y phosphatase	Protein-tyrosine phosphatase	4.8e-299	1006.8
25	SH3	SH3 domain	0.026	5.2
32	ig	Immunoglobulin domain	1.8e-09	35.6
37	7tm_3	7 transmembrane receptor	7.2e-09	29.0
<del>37</del> 39	ig	Immunoglobulin domain	1.4e-20	71.3
<del>40</del>	ig	Immunoglobulin domain	2.6e-15	54.4
45	SH3	SH3 domain	1.4e-42	154.9
<del>43</del> —		Immunoglobulin domain	2.5e-16	57.7
<del>47</del> 48	ig ig	Immunoglobulin domain	1.6e-24	84.1
65	zf-C2H2	Zinc finger, C2H2 type	2.7e-06	34.3
<del>66</del>	TGF-beta	Transforming growth factor beta like	6.9e-64	197.9
73	Ribosomal_L20	Ribosomal protein L20	2e-22	74.0
<del>79</del>	connexin	Connexin	1.6e-50	181.3
96	ig	Immunoglobulin domain	2.5e-26	89.9
<del>97</del>	ig	Immunoglobulin domain	1.5e-08	32.6
98	ig	Immunoglobulin domain	3.6e-25	86.1
99	ig	Immunoglobulin domain	7.6e-33	110.9
102	FG-GAP	FG-GAP repeat	6.9e-66	232.3
107	ig	Immunoglobulin domain	1.3e-16	58.6
107	thiored	Thioredoxin	2.8e-79	267.1
109	ig	Immunoglobulin domain	2.9e-16	57.5
$\frac{109}{110}$	ig	Immunoglobulin domain	4.6e-13	47.1
$\frac{110}{111}$	laminin G	Laminin G domain	2.4e-63	223.9
112	laminin_G	Laminin G domain	2.4e-63	223.9
114	LBP BPI_CETP	LBP / BPI / CETP family	2.6e-06	-2.4
116	efhand	EF hand	1.1e-14	62.2
118	SAP	SAP domain	4.8e-12	53.5
121	ig	Immunoglobulin domain	2.9e-16	57.5
129	zf-C2H2	Zinc finger, C2H2 type	1.7e-64	227.7
139	HSF DNA-bind	HSF-type DNA-binding domain	1.7e-05	22.3
140	7tm_l	7 transmembrane receptor (rhodopsin family)	1.1e-15	52.0
1.41	+;	Immunoglobulin domain	9.4e-09	33.3
141 145	MHC_II_beta	Class II histocompatibility antigen, beta	2.7e-29	110.7

SEQ	PFAM NAME	DESCRIPTION	p-value	PFAM
ID				SCORE
NO:				
	fibrinogen_C	Fibrinogen beta and gamma chains,	1.3e-35	125.6
	<u> </u>	C-term		
154	ig	Immunoglobulin domain	6.7e-05	20.8
155	ig	Immunoglobulin domain	0.00022	19.2
158	ig	Immunoglobulin domain	7e-19	65.9
159	ig	Immunoglobulin domain	3.5e-28	95.9
160	ig	Immunoglobulin domain	2.4e-06	25.5
162	3Beta_HSD	3-beta hydroxysteroid	1e-199	676.9
102	3Dotta_113D	dehydrogenase/isomera	ļ	
164	ig	Immunoglobulin domain	2.1e-09	35.3
169	p450	Cytochrome P450	8.9e-141	481.1
170	p450	Cytochrome P450	2.1e-131	450.0
171	p450	Cytochrome P450	1.7e-112	387.1
173	FKBP	FKBP-type peptidyl-prolyl cis-trans	5.1e-27	89.2
173	IKDI	isomeras		
174	sugar_tr	Sugar (and other) transporter	0.014	-120.6
187	CUB	CUB domain	2.2e-56	200.7
189	Apolipoprotein	Apolipoprotein A1/A4/E family	1.6e-06	34.6
191	ig	Immunoglobulin domain	1.7e-24	84.0
192	SPRY	SPRY domain	6.2e-13	56.4
192	fer4	4Fe-4S binding domain	1.6e-13	58.4
199	ank	Ank repeat	2.7e-09	44.3
209	zf-DHHC	DHHC zinc finger domain	4.6e-24	93.4
210	ATPIGI_PLM_MAT8		9.3e-22	85.7
211	Kelch	Kelch motif	0.02	20.8
212	DEAD	DEAD/DEAH box helicase	2.8e-52	168.3
213	DEAD	DEAD/DEAH box helicase	2.8e-52	168.3
		Kunitz/Bovine pancreatic trypsin	3.7e-47	148.6
214	Kunitz_BPTI	inhibito		l
215	Acyltransferase	Acyltransferase	0.0023	4.4
		Immunoglobulin domain	1.7e-10	38.9
216	ig	Immunoglobulin domain	1.1e-08	33.1
217	ig	Spectrin repeat	0	1209.7
218	spectrin	PH domain	5.3e-08	33.6
219	PH As trans	Transmembrane amino acid	1.5e-21	85.0
220	Aa_trans	transporter protein	1	
222	of C2UC4	Zinc finger, C3HC4 type (RING	7.7e-07	26.4
223	zf-C3HC4	finger)	15	
334	DA .	PA domain	0.00022	28.0
224	PA	Kazal-type serine protease inhibitor	5.6e-13	56.6
227	kazal		3.00-13	30.0
225	TTD C	domain	4.7e-45	163.1
235	TBC	TBC domain	17.70-43	100.1

TABLE 5

SEQ ID NO:	POSITION OF SIGNAL IN AMINO ACID SEQUENCE	MaxS (MAXIMUM SCORE)	MeanS (MEAN SCORE)
1	1-16	0.907	0.635
2	1-45	0.970	0.723
3	1-31	0.970	0.770
4	1-25	0.929	0.655
5	1-28	0.990	0.860
6	1-18	0.977	0.916
7	1-22	0.990	0.921
8	1-45	0.973	0.605
9	1-22	0.991	0.915
10	1-18	0.910	0.637
11	1-20	0.997	0.915
12	1-21	0.967	0.949
13	1-22	0.985	0.949
14	1-29	0.932	0.690
15	1-15	0.933	0.831
16	1-19	0.985	0.932
17	1-21	0.996	0.951
18	1-18	0.942	0.764
19	1-18	0.954	0.725
20	1-29	0.891	0.625
21	1-31	0.992	0.895
22	1-18	0.974	0.820
23	1-46	0.994	0.917
24	1-32	0.983	0.865
26	1-22	0.975	0.874
27	1-19	0.943	0.723
28	1-21	0.971	0.925
30	1-31	0.970	0.770
31	1-26	0.958	0.844
32	1-19	0.959	0.930
34	1-41	0.958	0.553
35	1-11	0.888	0.610
	1-29	0.888	0.611
36	1-32	0.917	0.567
38	1-27	0.978	0.895
39	1-27	0.929	0.655
40		0.972	0.946
44	1-21	0.972	0.806
46	1-28	0.985	0.892
47	1-19	0.981	0.955
48	1-19	0.981	0.675
49	1-21		0.920
52	1-23	0.976	0.920
53	1-19	0.988	0.782
55	1-15	0.901	0.782
58	1-24	0.953	0.772
59	1-32	0.992	0.743

SEQ ID NO:	POSITION OF SIGNAL IN AMINO ACID SEQUENCE	MaxS (MAXIMUM SCORE)	MeanS (MEAN SCORE)
61	1-19	0.896	0.566
62	1-37	0.915	0.693
66	1-22	0.978	0.889
67	1-24	0.922	0.563
68	1-18	0.962	0.763
69	1-31	0.990	0.773
70	1-21	0.902	0.802
71	1-31	0.922	0.604
72	1-22	0.932	0.645
74	1-32	0.947	0.669
75	1-20	0.973	0.832
76	1-24	0.933	0.597
77	1-42	0.964	0.719
79	1-45	0.973	0.605
82	1-18	0.975	0.870
83	1-25	0.990	0.919
85	1-18	0.946	0.753
87	1-20	0.976	0.854
89	1-27	0.990	0.907
90	1-23	0.890	0.717
92	1-40	0.881	0.660
93	1-36	0.886	0.568
95	1-41	0.994	0.804
96	1-19	0.975	0.901
97	1-19	0.975	0.901
98	1-19	0.975	0.901
99	1-19	0.975	0.901
100	1-18	0.990	0.955
101	1-36	0.998	0.907
102	1-22	0.932	0.756
103	1-15	0.928	0.793
104	1-45	0.992	0.911
105	1-20	0.988	0.926
107	1-19	0.985	0.892
109	1-15	0.983	0.953
110	1-16	0.969	0.894
113	1-19	0.941	0.828
114	1-20	0.989	0.973
115	1-23	0.960	0.786
117	1-22	0.886	0.663
119	1-18	0.960	0.820
120	1-16	0.924	0.582
121	1-16	0.987	0.929
122	1-22	0.992	0.956
123	1-23	0.929	0.588
126	1-41	0.968	0.792
127	1-34	0.930	0.665

SEQ ID NO:	POSITION OF SIGNAL IN AMINO ACID SEQUENCE	MaxS (MAXIMUM SCORE)	MeanS (MEAN SCORE)
128	1-42	0.957	0.653
130	1-21	0.897	0.632
131	1-25	0.983	0.845
132	1-13	0.947	0.915
133	1-13	0.930	0.824
134	1-22	0.947	0.857
135	1-25	0.978	0.936
137	1-17	0.960	0.878
141	1-16	0.983	0.952
142	1-23	0.945	0.798
145	1-29	0.979	0.884
146	1-25	0.922	0.765
147	1-37	0.928	0.786
148	1-28	0.981	0.890
150	1-20	0.986	0.965
151	1-20	0.987	0.886
152	1-18	0.922	0.809
153	1-19	0.887	0.607
154	1-16	0.964	0.790
155	1-17	0.984	0.973
156	1-21	0.929	0.692
157	1-21	0.937	0.836
158	1-19	0.897	0.722
159	1-19	0.985	0.932
160	1-21	0.978	0.833
161	1-20	0.940	0.632
165	1-20	0.954	0.696
167	1-20	0.988	0.963
168	1-20	0.986	0.952
169	1-8	0.983	0.634
170	1-8	0.983	0.634
171	1-40	0.994	0.888
173	1-27	0.982	0.925
174	1-17	0.989	0.945
176	1-21	0.987	0.919
177	1-21	0.950	0.596
178	1-22	0.986	0.949
179	1-18	0.942	0.764
181	1-16	0.917	0.618
182	1-23	0.963	0.889
183	1-25	0.992	0.968
184	1-19	0.945	0.638
185	1-31	0.964	0.709
186	1-37	0.978	0.830
187	1-27	0.947	0.799
190	1-41	0.972	0.836
193	1-16	0.900	0.664

SEQ ID NO:	POSITION OF	MaxS (MAXIMUM	MeanS (MEAN
	SIGNAL IN AMINO	SCORE)	SCORE)
	ACID SEQUENCE		
194	1-35	0.988	0.912
195	1-16	0.944	0.837
196	1-28	0.925	0.626
197	1-20	0.962	0.811
198	1-21	0.947	0.701
199	1-20	0.945	0.854
200	1-34	0.967	0.718
201	1-32	0.994	0.956
203	1-18	0.953	0.786
204	1-24	0.968	0.728
205	1-32	0.920	0.623
206	1-27	0.974	0.843
208	1-31	0.986	0.878
209	1-29	0.997	0.854
214	1-19	0.986	0.967
215	1-37	0.981	0.952
216	1-18	0.974	0.820
217	1-18	0.974	0.820
218	1-21	0.937	0.819
219	1-31	0.914	0.554
224	1-21	0.981	0.945
225	1-25	0.938	0.890
227	1-22	0.965	0.891
230	1-23	0.884	0.746
231	1-14	0.885	0.675
232	1-20	0.930	0.729

TABLE 6

SEQ ID	SEQ ID	SEQ ID	SEQ ID	Priority docket	SEQ ID NO:
NO: of full-	NO: of	NO: of	NO: of	number_corresponding	in U.S.S.N.
length	full-length	contig	contig	SEQ ID NO: in priority	09/491,404
nucleotide	peptide	nucleotide	peptide	application	
sequence	sequence	sequence	sequence		
1	237	473	709	785CIP2B_1	10
2	238	474	710	785CIP2B_2	449
3	239	475	711	785CIP2B_3	1376
4	240	476	712	785CIP2B_4	1425
5	241	477	713	785CIP2B_5	1472
6	242	478	714	785CIP2B_6	1503
7	243	479	715	785CIP2B_7	1513
8	244	480	716	785CIP2B_8	1518
9	245	481	717	785CIP2B_9	1525
10	246	482	718	785CIP2B_10	1533
11	247	483	719	785CIP2B_11	1537
12	248	484	720	785CIP2B_12	1542
13	249	485	721	785CIP2B_13	1549
14	250	486	722	785CIP2B_14	1560
15	251	487	723	785CIP2B 15	1715
16	252	488	724	785CIP2B 16	1731
17	253	489	725	785CIP2B_17	1757
18	254	490	726	785CIP2B 18	1791
19	255	491	727	785CIP2B 19	1809
20	256	492	728	785CIP2B 20	1818
21	257	493	729	785CIP2B_21	1857
22	258	494	730	785CIP2B_22	1869
23	259	495	731	785CIP2B_23	1905
24	260	496	732	785CIP2B_24	1910
25	261	497	733	785CIP2B_25	1917
26	262	498	734	785CIP2B_26	1924
27	263	499	735	785CIP2B_27	1937
28	264	500	736	785CIP2B_28	1965
29	265	501	737	785CIP2B_29	2033
30	266	502	738	785CIP2B_30	2035
31	267	503	739	785CIP2B_31	2194
32	268	504	740	785CIP2B_32	2195
33	269	505	741	785CIP2B 33	2197
34	270	506	742	785CIP2B_34	2199
35	271	507	743	785CIP2B 35	2201
36	272	508	744	785CIP2B 36	2201
37	273	509	745	785CIP2B 37	2253
38	274	510	746	785CIP2B 38	2257
39	275	511	747	785CIP2B 39	2264
40	276	512	748	785CIP2B 40	2264
41	277	513	749	785CIP2B 41	2266
42	278	514	750	785CIP2B 42	2272
43	279	515	751	785CIP2B 43	2272
44	280	516	752	785CIP2B 44	2274
L.:	1200	1	J.:		_ <del></del>

SEQ ID	SEQ ID	SEQ ID	SEQ ID	Priority docket	SEQ ID NO:
NO: of full-	NO: of	NO: of	NO: of	number_corresponding	in U.S.S.N.
length	full-length	contig	contig	SEQ ID NO: in priority	09/491,404
nucleotide	peptide	nucleotide	peptide	application	
sequence	sequence	sequence	sequence		
45	281	517	753	785CIP2B_45	2283
46	282	518	754	785CIP2B_46	2285
47	283	519	755	785CIP2B_47	2289
48	284	520	756	785CIP2B_48	2294
49	285	521	757	785CIP2B_49	2295
50	286	522	758	785CIP2B_50	2297
51	287	523	759	785CIP2B_51	2301
52	288	524	760	785CIP2B_52	2312
53	289	525	761	785CIP2B_53	2313
54	290	526	762	785CIP2B_54	2324
55	291	527	763	785CIP2B_55	2337
56	292	528	764	785CIP2B_56	2338
57	293	529	765	785CIP2B_57	2345
58	294	530	766	785CIP2B_58	2359
59	295	531	767	785CIP2B_59	2361
60	296	532	768	785CIP2B_60	2369
61	297	533	769	785CIP2B_61	2379
62	298	534	770	785CIP2B 62	2382
63	299	535	771	785CIP2B 63	2389
64	300	536	772	785CIP2B 65	2400
65	301	537	773	785CIP2B 66	2411
66	302	538	774	785CIP2B 67	2422
67	303	539	775	785CIP2B 68	2425
68	304	540	776	785CIP2B 69	2426
69	305	541	777	785CIP2B 70	2428
70	306	542	778	785CIP2B 71	2431
71	307	543	779	785CIP2B 72	2440
72	308	544	780	785CIP2B 73	2443
73	309	545	781	785CIP2B 74	2451
74	310	546	782	785CIP2B 75	2458
75	311	547	783	785CIP2B 76	2462
76	312	548	784	785CIP2B 77	2470
77	313	549	785	785CIP2B 78	2487
78	314	550	786	785CIP2B 79	2497
79	315	551	787	785CIP2B 80	2504
80	316	552	788	785CIP2B 81	2510
81	317	553	789	785CIP2B 82	2513
82	318	554	790	785CIP2B 83	2519
83	319	555	791	785CIP2B 84	2520
84	320	556	792	785CIP2B 85	2524
85	321	557	793	785CIP2B 86	2528
86	322	558	794	785CIP2B 87	2531
87	323	559	795	785CIP2B 88	2558
	323	560	796	785CIP2B 89	2567
88		561	797	785CIP2B 90	2584
90	325	562	797	785CIP2B 91	2588

SEQ ID	SEQ ID	SEQ ID	SEQ ID	Priority docket	SEQ ID NO:
NO: of full-	NO: of	NO: of	NO: of	number_corresponding	in U.S.S.N.
length	full-length	contig	contig	SEQ ID NO: in priority	09/491,404
nucleotide	peptide	nucleotide	peptide	application	
sequence	sequence	sequence	sequence		
91	327	563	799	785CIP2B 92	2594
92	328	564	800	785CIP2B 93	2596
93	329	565	801	785CIP2B 94	2599
94	330	566	802	785CIP2B 95	2601
95	331	567	803	785CIP2B 96	2603
96	332	568	804	785CIP2B 97	2604
97	333	569	805	785CIP2B 98	2604
98	334	570	806	785CIP2B 99	2604
99	335	571	807	785CIP2B 100	2604
100	336	572	808	785CIP2B 101	2610
101	337	573	809	785CIP2B 102	2612
102	338	574	810	785CIP2B 103	2626
103	339	575	811	785CIP2B 104	2629
104	340	576	812	785CIP2B 105	2630
105	341	577	813	785CIP2B 106	2631
106	342	578	814	785CIP2B 107	2639
107	343	579	815	785CIP2B 108	2651
108	344	580	816	785CIP2B 109	2652
109	345	581	817	785CIP2B 110	2661
110	346	582	818	785CIP2B 111	2662
111	347	583	819	785CIP2B 112	2677
112	348	584	820	785CIP2B 113	2677
113	349	585	821	785CIP2B 114	2680
114	350	586	822	785CIP2B 115	2688
115	351	587	823	785CIP2B 116	2693
116	352	588	824	785CIP2B 117	2716
117	353	589	825	785CIP2B 118	2720
118	354	590	826	785CIP2B 119	2721
119	355	591	827	785CIP2B 120	2724
120	356	592	828	785CIP2B 121	2725
121	357	593	829	785CIP2B 122	2727
122	358	594	830	785CIP2B 123	2739
123	359	595	831	785CIP2B 124	2740
124	360	596	832	785CIP2B 125	2747
125	361	597	833	785CIP2B 126	2748
126	362	598	834	785CIP2B 127	2752
127	363	599	835	785CIP2B_127	2755
128	364	600	836	785CIP2B_128	2764
129	365	601	837	785CIP2B_129 785CIP2B 130	2773
130	366	602	838	785CIP2B_130	2778
131	367	603	839	785CIP2B_131 785CIP2B_132	2779
131		604			
132	368	<u></u>	840	785CIP2B_133	2780
	369	605	841	785CIP2B_134	2781
134	370	606	842	785CIP2B_135	2786
135	371	607	843	785CIP2B_136	2790
136	372	608	844	785CIP2B_137	2791

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SEQ ID	SEQ ID	SEQ ID	SEQ ID	Priority docket	SEQ ID NO:
NO: of full-	NO: of	NO: of	NO: of	number_corresponding	in U.S.S.N.
length	full-length	contig	contig	SEQ ID NO: in priority	09/491,404
nucleotide	peptide	nucleotide	peptide	application	
sequence	sequence	sequence	sequence	50.60VPQP 120	2705
137	373	609	845	785CIP2B_138	2795
138	374	610	846	785CIP2B_139	2801
139	375	611	847	785CIP2B_140	2802
140	376	612	848	785CIP2B_141	2804
141	377	613	849	785CIP2B_142	2811
142	378	614	850	785CIP2B_143	2820
143	379	615	851	785CIP2B_144	2825
144	380	616	852	785CIP2B_145	2836
145	381	617	853	785CIP2B_146	2841
146	382	618	854	785CIP2B_147	2843
147	383	619	855	785CIP2B_148	2844
148	384	620	856	785CIP2B_149	2845
149	385	621	857	785CIP2B_150	2849
150	386	622	858	785CIP2B_151	2850
151	387	623	859	785CIP2B_152	2866
152	388	624	860	785CIP2B_153	2873
153	389	625	861	785CIP2B_154	2874
154	390	626	862	785CIP2B_155	2878
155	391	627	863	785CIP2B_156	2882
156	392	628	864	785CIP2B 157	2888
157	393	629	865	785CIP2B 158	2894
158	394	630	866	785CIP2B 159	2899
159	395	631	867	785CIP2B 160	2899
160	396	632	868	785CIP2B_161	2903
161	397	633	869	785CIP2B 162	2905
162	398	634	870	785CIP2B 163	2913
163	399	635	871	785CIP2B 164	2920
164	400	636	872	785CIP2B 165	2927
165	401	637	873	785CIP2B 166	2938
	401	638	874	785CIP2B 167	2952
166		639	875	785CIP2B_168	2954
167	403		876	785CIP2B 169	2954
168	404	640	877	785CIP2B 170	2958
169	405	641	878	785CIP2B_171	2958
170	406	642	879	785CIP2B 172	2958
171	407	643	880	785CIP2B 173	2959
172	408	644		785CIP2B 174	2961
173	409	645	881	785CIP2B_174	2978
174	410	646	882		2981
175	411	647	883	785CIP2B_176	2996
176	412	648	884	785CIP2B_177	
177	413	649	885	785CIP2B_178	2997
178	414	650	886	785CIP2B_179	3001
179	415	651	887	785CIP2B_180	3006
180	416	652	888	785CIP2B_181	3007
181	417	653	889	785CIP2B_182	3010
182	418	654	890	785CIP2B_183	3034

SEQ ID	SEQ ID	SEQ ID	SEQ ID	Priority docket	SEQ ID NO:
NO: of full-	NO: of	NO: of	NO: of	number corresponding	in U.S.S.N.
length	full-length	contig	contig	SEQ ID NO: in priority	09/491,404
nucleotide	peptide	nucleotide	peptide	application	
sequence	sequence	sequence	sequence	11	
183	419	655	891	785CIP2B 184	3058
184	420	656	892	785CIP2B 185	3060
185	421	657	893	785CIP2B 186	3061
186	422	658	894	785CIP2B 187	3078
187	423	659	895	785CIP2B 188	3081
188	424	660	896	785CIP2B 189	3083
189	425	661	897	785CIP2B 190	3086
190	426	662	898	785CIP2B 191	3090
191	427	663	899	785CIP2B 193	3102
192	428	664	900	785CIP2B 194	3110
193	429	665	901	785CIP2B 195	3117
194	430	666	902	785CIP2B 196	3118
195	431	667	903	785CIP2B 197	3121
196	432	668	904	785CIP2B 198	3124
197	433	669	905	785CIP2B 199	3131
198	434	670	906	785CIP2B 200	3132
199	435	671	907	785CIP2B 201	3135
200	436	672	908	785CIP2B 202	3143
201	437	673	909	785CIP2B 203	3145
202	438	674	910	785CIP2B 204	3156
203	439	675	911	785CIP2B 205	3160
204	440	676	912	785CIP2B 206	3163
205	441	677	913	785CIP2B 207	3167
206	442	678	914	785CIP2B 208	3170
207	443	679	915	785CIP2B 209	3174
208	444	680	916	785CIP2B 210	3176
209	445	681	917	785CIP2B 211	3178
210	446	682	918	785CIP2B 212	3180
211	447	683	919	785CIP2B 213	3791
212	448	684	920	785CIP2B 215	3793
213	449	685	921	785CIP2B 216	3793
214	450	686	922	785CIP2B 217	3794
215	451	687	923	785CIP2B 218	3795
216	452	688	924	785CIP2B 219	3796
217	453	689	925	785CIP2B 220	3796
218	454	690	926	785CIP2C_1	145
219	455	691	927	785CIP2C 3	639
220	456	692	928	785CIP2C 4	652
221	457	693	929	785CIP2C 5	753
222	458	694	930	785CIP2C 6	754
223	459	695	931	785CIP2C 7	1258
224	460	696	932	785CIP2C 8	1316
225	461	697	933	785CIP2C 9	1343
226	462	698	934	785CIP2C 11	1499
227	463	699	935	785CIP2C 12	1659
228	464	700	936	785CIP2C 13	2024
120	107	L,00	730	1/03011/20_13	2024

SEQ ID	SEQ ID	SEQ ID	SEQ ID	Priority docket	SEQ ID NO:
NO: of full-	NO: of	NO: of	NO: of	number_corresponding	in U.S.S.N.
length	full-length	contig	contig	SEQ ID NO: in priority	09/491,404
nucleotide	peptide	nucleotide	peptide	application	
sequence	sequence	sequence	sequence		
229	465	701	937	785CIP2C_15	2114
230	466	702	938	785CIP2C_16	2119
231	467	703	939	785CIP2C_17	2126
232	468	704	940	785CIP2C_19	2137
233	469	705	941	785CIP2C_20	2143
234	470	706	942	785CIP2C_21	2145
235	471	707	943	785CIP2C_22	2853
236	472	708	944	785CIP2C_24	3076

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## TABLE 7

SEQ ID	Predicted	Predicted end	Amino said assment containing signal mentids
NO:	beginning	nucleotide	Amino acid segment containing signal peptide (A=Alanine C=Cysteine, D=Aspartic Acid,
140.	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	
	acid residue	amino acid	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	E .	4	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
700	sequence	201	deletion, \=possible nucleotide insertion
709	465	301	MGKSLASQFPITLIFSAFSSTFCLLDGLFISCPCT
710	1101	1345	STELPKVNSLLSRPESATT*
710	1181	1345	MLALSSSFLVLSYLLTRWCGSVGFILANCFNM
711	106	701	GIRITQSLCFIHRYYRRSPHRPL
711	186	701	MKVLWAALLVTFLAGCQAKVEQAVETEPEPE
			LRQQTEWQSGQRWELALGRFWDYLRWVQTLS
			EQVQEELLSSQVTQELRALMDETMKELKAYKS
			ELEEQLTPVAEETRARLSKELQAAQARLGADM
			EDVCGRLGAVTAVMVQGHARPEQPRSCGWRV
			RLPPAQAGVSGSLR*
712	3917	4081	MFRRLTFAQLLFATVLGIAGGVYIFQPVFEQYA
			KDQKELKEKMQLVQESEEKKS*
713	26	1123	MSLLGFLLSRLGLLLKVLLDWPVEVLYGAAAL
			NGLFGGFSAFWSGVMALGSLGSSEGRRSVRLIL
			IDLMLGLAGFCGSMASGHLFKQMAGHSGQGLI
			LTACSVSCASFALLYSLLVLKVPESVAKPSQEL
			PAVDTVSGTVGTYRTLDPDQLDQQYAVGHPPS
			PGKAKPHKTTIALLFVGAIIYDLAVVGTVDVIPL
			FVLREPLGWNQVQVGYGMAAGYTIFITSFLGV
			LVFSRCFRDTTMIMIGMVSFGSGALLLAFVKET
			YMFYIARAVMLFALIPVTTIRSAMSKLIKGSSY
			GKVFVILQLSLALTGVVTSTLYNKIYQLTMDM
			FGGSCFALSSFLSFLAIIPISIVAYKQVPLSPYGDI
			IEK*
714	39	431	MFLFLFFLVAILPVNTEGGEIIWGTESKPHSRPY
			MAFIKFYDSNSEPHHCGGFLVAKDIVMTAAHC
			NGRNIKVTLGAHNIKKQENTQVISVVKAKPHE
•			NYDRDSHFNDIMLLKLERKAQLNGCCEDYCPS
			*
715	970	1755	MLVLLVLRVSLAALVKMELLVRWAPVACLVR
			EVALEPLALLVLVEMMVLLVLPGPLVPPAPLV
			LLASLVLLVLRVKLVPKGPEALKVPRVCVVSL
			APLALLVLLALLETLVLRESLVLKVPMVLLVLL
			VLLASLVPEAPLDPRAPAALLVPRVTAVNLVLL
			AAKETLVLRESLALLVFKDPLALLERKESEELE
			VNPDPLACPDPLASVVDLVAVVSLAQMVLLVP
			RVPLVNVVLLALLAPKDLLVKLVVPVKLVCLV
			PRV*
716	3060	2899	MMLLVSLHILFPFMPFSYGLESNNSKPQCLMKL
			TLQNLQKQVAFEVFSHTKYN*
717	70	618	MGWTMRLVTAALLLGLMMVVTGDEDENSPC

SEQ ID	Predicted	Predicted end	Amino acid acoment containing signal montide
NO:	beginning	nucleotide	Amino acid segment containing signal peptide
NO:	nucleotide	location	(A=Alanine C=Cysteine, D=Aspartic Acid,
	1		E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
ļ	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence		deletion, \=possible nucleotide insertion
		,	AHEALLDEDTLFCQGLEVFYPELGNIGCKVVPD
]			CNNYRQKITSWMEPIVKFPGAVDGATYILVMV
			DPDAPSRAEPRQRFWRHWLVTDIKGADLKEGK
			IQGQELSALPGSLPHRHTVAFHRYQVLCLSSGR
			EKSSLSFPRKTKLEALGKWTDF*
718	79	342	MRRSFWTVMRTAWRCSCSSVDRALSHQAGLQ
			GQCLSACLLGNLGYPPFISPPAQVLCAARASCH
			LGSLMAHFETLVHSKDWSCVILK*
719	382	1326	MLFWVLGLLILCGFLWTRKGKLKIEDITDKYIFI
			TGCDSGFGNLAARTFDKKGFHVIAACLTESGST
		<u> </u>	ALKAETSERLRTVLLDVTDPENVKRTAQWVK
Į			NOVGEKGLWGLINNAGVPGVLAPTDWLTLED
		•	YREPIEVNLFGLISVTLNMLPLVKKAQGRVINV
			SSVGGRLAIVGGGYTPSKYAVEGFNDSLRRDM
			KAFGVHVSCIEPGLFKTNLADPVKVIEKKLAIW
			EQLSPDIKQQYGEGYIEKSLDKLKGNKSYVNM
			DLSPVVECMDHALTSLFPKTHYAAGKDAKIFW
			IPLSHMPAALQDFLLLKQKARAG*
720	875	516	MSVPTMAWMMLLLGLLAYGSGVESQTVVTQE
			PSLSVSPGGTVTLTCGLTSGSVSTSFYPSWYQQ
			TPGQAPRTLIYSTNTRSSGVPGRFSGSILGSKAA
			LTITGAQADDESDYYCVLICR*
721	431	3643	MNCDVLWCVLLLVCMSLFSAVGHGLWIWRY
1			QEKKSLFYVPKSDGSSLSPVTAAVYSFLTMIIVL
			QVLIPISLYVSIEIVKACQVYFINQDMQLYDEET
			DSQLQCRALNITEDLGQIQYIFSDKTGTLTENK
		}	MVFRRCTVSGVEYSHDANAQRLARYQEADSE
			EEEVVPRGGSVSQRGSIGSHQSVRVVHRTQSTK
			SHRRTGSRAEAKRASMLSKHTAFSSPMEKDITP
			DPKLLEKVSECDKSLAVARHQEHLLAHLSPELS
			DVFDFLIALTICNTVVVTSPDQPRTKVRVRFEL
			KSPVKTIEDFLRRFTPSCLTSGCSSIGSLAANKSS
			HKLGSSFPSTPSSDGMLLRLEERLGQPTSAIASN
			GYSSQADNWASELAQEQESERELRYEAESPDE
		1	AALVYAARAYNCVLVERLHDQVSVELPHLGR
			LTFELLHTLGFDSVRKRMSVVIRHPLTDEINVY
			TKGADSVVMDLLQPCSSVDARGRHQKKIRSKT
			QNYLNVYAAEGLRTLCIAKRVLSKEEYACWLQ
			SHLEAESSLENSEELLFQSAIRLETNLHLLGATG
		]	IEDRLQDGVPETISKLRQAGLQIWVLTGDKQET
		1	AVNIAYACKLLDHDEEVITLNATSQEACAALL
		1	
		1	DQCLCYVQSRGPQRAPEKTKGKVSMRFSSLCP
1	1	1	PSTSTASGRRPSLVIDGRSMAYALEKNLEDKFL

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence	1	deletion, \=possible nucleotide insertion
	<u> </u>		FLAKQCRSVLCCRSTPLQKSMVVKLVRSKLKA
			MTLAIGDGANDVSMIQVADVGVGISGQEGMQ
			AVMASDFAVPKFRYLERLLILHGHWCYSRLAN
			MVLYFFYKNTMFVGLLFWFQFFCGFSASTMID
İ			QWYLIFFNLLFSSLPPLVTGVLDRDVPANVLLT
İ	Ì		NPQLYKSGQNMEEYRPRTFWFNMADAAFOSL
			VCFSIPYLAYYDSNVDLFTWGTPIVTIALLTFLL
			HLGIETKTWTWLNWITCGFSVLLFFTVALIYNA
1			SCATCYPPSNPYWTMQALLGDPVFYLTCLMTP
			VAALLPRLFFRSLQGRVFPTQLQLARQLTRKSP
İ			RRCSAPKETFAQGRPXEGLGNRGTHQGGQSRP
			LCPCPSLLGTHSSRSAPWRPAGSPAQWT*
722	3616	1673	MLWVTGPVLAVILIILIVIAILLFKRKRTHSPSSK
			DEQSIGLKDSLLAHSSDPVEMRRLNYQTPGMR
			DHPPIPITDLADNIERLKANDGLKFSQEYESIDP
			GQQFTWENSNLEVNKPKNRYANVIAYDHSRVI
1			LTSIDGVPGSDYINANYIDGYRKQNAYIATQGP
			LPETMGDFWRMVWEQRTATVVMMTRLEEKS
			RVKCDQYWPARGTETCGLIQVTLLDTVELATY
			TVRTFALHKSGSSEKRELRQFQFMAWPDHGVP
	·		EYPTPILAFLRRVKACNPLDAGPMVVHCSAGV
			GRTGCFIVIDAMLERMKHEKTVDIYGHVTCMR
			SQRNYMVQTEDQYVFIHEALLEAATCGHTEVP
1			ARNLYAHIQKLGQVPPGESVTAMELEFKLLASS
			KAHTSRFISANLPCNKFKNRLVNIMPYELTRVC
			LQPIRGVEGSDYINASFLDGYRQQKAYIATQGP
			LAESTEDFWRMLWEHNSTIIVMLTKLREMGRE
	·		KCHQYWPAERSARYQYFVVDPMAEYNMPQYI
	,		LREFKVTDARDGQSRTIRQFQFTDWPEQGVPK
	,		TGEGFIDFIGQVHKTKEQFGQDGPITVHCSAGV
1			GRTGVFITLSIVLERMRYEGVVDMFQTVKTLRT
			QRPAMVQTEDQYQLCYRAALEYLGSFDHYAT
723	484	765	MINIVEACIEODI III IDCVCCA DOVICOCCI A CONTR
123	707	103	MIWIYFAFIFQRLHLIPGKSSARQVSGFSLLSFNP
			SNTIFVKLDWWCFIQLIYSAYLFEKRLLEIDDVF
724	846	983	VPVILKVVGARIEFHSGIGFGSGL*
/ <del>~</del> ₹	070	703	MLIAVIACICYLSLLHSYDILFGHFSVLSQGLDK
725	154	513	HCLTLFLSLGG*
123	137	213	MVIINCSPRFWFLFPFTIQHTCKCPLGVRYHTRH
			LEQIAANKKHCPYPYEVHYNSSYWRAGIILHTL
			HAYLTSYPHYYSFFFFFGKGVPFCPQGGGAGK
726	709	566	GSGLMGSHRGTKPKSFLKKK
.20	. 07	200	MERHGFFLDVCLILGLIPLSIKYSLQKRGKNSA

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NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue	amino acid	V-Voline W-Trustenham W-Trust
	of amino acid	i	V=Valine, W=Tryptophan, Y=Tyrosine,
	1	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
ļ	sequence		deletion, \=possible nucleotide insertion
727	175	342	ADNAGWSDLSLGQN*
121	173	342	MYMNTCLYLHVYVLTCSGCNVDMCSRLFLST
728	109	264	KLKAHVQIVLYWVFLWSRGNNFLT*
120	109	204	MVILDVLELYHMWFLGILYDAIFYCFVHAINA
729	56	220	DKFFGLKLTKSATVSQNSQ*
129	36	220	MYDFLLLLSFIFIVASYWSFLSTIFLDVVCSILHC
730	735	1025	PVKPQTLLKSCLHVDCKST*
/30	/33	1235	MVGLGGMSQLLLASLLPPVPQGSPTRRKLPASL
			LVSTALISPVCVRGWMWQNLQNRIHGSHTSAR
			RVPSLPGAGQVGVRWEAGPACRTQPSPQNLAP
			RPHPSAAQLIENAALRSAMSGERLFPEGQEHLG
			PLVAPRVPMGGALCPPLPSLSCAICKVGAAREA
731	109	202	GGR*
/31	109	303	MKPYCMYPFLSGLLSSLLFWVESLMLLCVQMV
732	165	250	LFLMLCVLDYRIYCIKIYVSIILLMSIWIISI*
132	100	359	MCYFYNTIILTLQGSLMFLLFSVVTLYLFSHSHP
722	7	0.70	TPISIFSDVFNMYPWIYMYSYMVFSVNLYK*
733	7	279	MAAAPGLLVWLLVLRLPWRVPGQLDPSTGRR
			FSEHKLCADDECSMLMYRGEALEDFTGPDCRF
734	81	076	VNFKKGDPVYVYYKLARGWPEVWAGSK*
734	81	275	MPGYVPLLLLLLLRCSQRGGGVNFGEKDAKV
	· '		PGTWRDGVRVPGEGASWDSDRASPERRYGIGE
735	207	410	
733	207	419	MKFLLMSLPYRHLFCITQAILSEIAEGIRNDPFK
			FYLYSVLALFLHYYMYVFVSRFSIYYLKLLRIF
736	233	467	KFS*
730	233	457	MRQIAVFQRFMFPFLLPWLSCIFSSSQNSIYYVS
		•	TFIKCLALKSIIKRQRSEINSGFLAIYHALRNQVT
737	39	261	RCGGL*
131	39	251	MPRRTRGGLWLCNAHKSCQKYLSSLKLSTLLS
			PLLVLPFYTPSLKGWGIFVLRFYFMVIIADCNLF
738	155	212	KIII*
130	133	313	MFTHWLGPPVYIKQFIVMIVSILTLFPVLQGML
739	60	272	RNFLYLNIMFVVALLKAIL*
137	UU	272	MERGAGAKLLPLLLLRATGFTCAQADGRNG
			YTAVIEVTSGGPWGDWAWPEMCPDGFFASGFS
740	40	260	LKVGAQA*
/40	49	360	MTQVERVIVFLTLSTLSLAKTTQPIFMDSYEGQ
			EVNITCSHNNIVTNDYITWYQQFPSQGPRFIIQG
			YQKKVTNEVAFLCIPADRKSITLNLPRVSLEDT
7/1	47	206	GGK*
741	47	325	MTKLAQWLWGLAILGSTWVALTTGALGLELP
	<del></del>		LSCQEVLWPLPAYLLVSAGCYALGTVGYRVAT

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
NO.	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location		
		corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence		deletion, \=possible nucleotide insertion
			FHDCEDAARELQSQIQEARADLARRGLRF*
742	301	438	MSVGLAGAVGRRCHLALAVLHDPLCHHGSLA
			TICKQPEVCLFTIV*
743	165	413	MPFLLNQCGSLLYYLTLASTDLTLAVPICNSLAI
			IFTLIVGKALGEDIGGKRAVAGMVLTVIGISLCI
			TSSVSKTQGQQSTL*
744	165	413	MPFLLNQCGSLLYYLTLASTDLTLAVPICNSLAI
			IFTLIVGKALGEDIGGKRAVAGMVLTVIGISLCI
ŀ			TSSVSKTQGQQSTL*
745	923	1618	MALIYVMLLLLGAFLGAWPALCGRYKRWRKH
			GVFVLLTTATSVAIWVVWIVMYTYGNKQHNS
i			PTWDDPTLAIALAANAWAFVLFYVIPEVSQVT
			KSSPEQSYQGDMYPTRGVGYETILKEQKGQSM
			FVENKAFSMDEPVAAKRPVSPYSGYNGQLLTS
			VYQPTEMALMHKVPSEGAYDIILPRATANSQV
			MGSANSTLRAEDMYSAQSHQAATPPKDGKNS
			QVFRNPYVWD*
746	14	370	MVKTDAHLKNPPFAPFRVYTLTLSLLLKLSHYS
/40	17	370	CLWVKKDFKDSSFYNSNNNSNSNHCKSLLSTH
			<u>-</u>
			YMPGAVISNLCLISCKVSSSPIKQTHGISMLQM
747	103	1002	KRLKHTLARLAPGTHGGSQN*
/4/	103	1002	MGTKAQVERKLLCLFILAILLCSLALGSVTVHS
			SEPEVRIPENNPVKLSCAYSGFSSPRVEWKFDQ
			GDTTRLVCYNNKITASYEDRVTFLPTGITFKSV
			TREDTGTYTCMVSEEGGNSYGEVKVKLIVLVP
			PSKPTVNIPSSATIGNRAVLTCSEQDGSPPSEYT
			WFKDGIVMPTNPKSTRAFSNSSYVLNPTTGELV
			FDPLSASDTGEYSCEARNGYGTPMTSNAVRME
			AVERNVGVIVAAVLVTLILLGILVFGIWFAYSR
			GHFDRTKKGTSSKKVIYSQPSARSEGEFKQTSS
6.15	100		FLV*
748	103	1002	MGTKAQVERKLLCLFILAILLCSLALGSVTVHS
			SEPEVRIPENNPVKLSCAYSGFSSPRVEWKFDQ
			GDTTRLVCYNNKITASYEDRVTFLPTGITFKSV
			TREDTGTYTCMVSEEGGNSYGEVKVKLIVLVP
			PSKPTVNIPSSATIGNRAVLTCSEQDGSPPSEYT
	İ		WFKDGIVMPTNPKSTRAFSNSSYVLNPTTGELV
			FDPLSASDTGEYSCEARNGYGTPMTSNAVRME
			AVERNVGVIVAAVLVTLILLGILVFGIWFAYSR
			GHFDRTKKGTSSKKVIYSQPSARSEGEFKQTSS
			FLV*
749	970	1263	MPSSFFLLLRFFLRIDGVLIRMNDTRLYHEADK
		. =	TYMLREYTSRESKISSLMHVPPSLFTEPNEISQY
			THE PROPERTY OF THE PROPERTY O

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NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
110.	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
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	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue	amino acid	V-Voling W-Triptonham V-T
	of amino acid	1	V=Valine, W=Tryptophan, Y=Tyrosine,
	1	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
ļ	sequence		deletion, \=possible nucleotide insertion
750	1207	007	LPIKEAVCEKLIFPERIDPNPADSQKSTQVE
/30	1207	887	MYTRELLAWIQGLYTWELLAWIQHLNTWELL
			PWIRRLNSWILLVCPKLLHLWVFGKTMEIFVLV
			KDMMPFLYKKELCLVPEVISLLIFSHLDTSKELS
251	1000		IYGLTQLI*
751	1207	887	MYTRELLAWIQGLYTWELLAWIQHLNTWELL
		•	PWIRRLNSWILLVCPKLLHLWVFGKTMEIFVLV
			KDMMPFLYKKELCLVPEVISLLIFSHLDTSKELS
			IYGLTQLI*
752	43	948	MFSHLPFDCVLLLLLLLTRSSEVEYRAEVGQN
			AYLPCFYTPAAPGNLVPVCWGKGACPVFECGN
			VVLRTDERDVNYWTSRYWLNGDFRKGDVSLT
			IENVTLADSGIYCCRIQIPGIMNDEKFNLKLVIK
			PAKVTPAPTLQRDFTAAFPRMLTTRGHGPAET
			QTLGSLPDINLTQISTLANELRDSRLANDLRDSG
			ATIRIGIYIGAGICAGLALALIFGALIFKWYSHSK
			EKIQNLSLISLANLPPSGLANAVAEGIRSEENIYT
			IEENVYEVEEPNEYYCYVSSRQQPSQPLGCRFA
			MP*
753	2350	2180	MGGVAFLLWLTVFSAWTRLSIFSRLSDLPSFCL
<u></u>		•	PLAGTVSSSLPEGSGCSFSSSTK*
754	369	707	MCHWQNSFLCQSFLTFGSILALLAGKACYPESE
	ĺ		SIRELFMWALELYSLPFYLFFKLSPLNLPGKLGL
			IETLSTCWGQKLDPVLETLQRVRSMASLIANFF
			VPFIQKKGQLIT*
755	847	149	MAWIPLFLGVLAYCTGSVASYELTQPPSVSVSP
			GQTASITCSGDNLGNKYVAWYQQKAGQSPVL
			VIYQDDKRPSEIPERFSGSNSGNTATLTISGTQA
•			MDEADYYCQAWDSSTAVMFGGGTKLTVLGQP
			KAAPSVTLFPPSSEELQANKATLVCLISDFYPGA
			VTVAWKADSSPVKAGVETTTPSKQSNNKYAA
			SSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTV
			APTECS*
756	1726	1869	MGAGCTPVVLGAALWLWRWFSRWGLGGLCW
			RPCTCTPCHSASPGAGR*
757	167	310	MLGICLCSICVLRLCLEKSKIFPPPRTSDHSLEGS
		· · ·	VTPVENAARSGM*
758	335	778	MSITRLFPALLECFVIVLCGYIAGRANVITSTQA
			KGLGNFVSRFALPALLFKNMVVLNFSNVDWAF
			LYSILIAKASVFFIVCVLTLLVASPDSRFSKAGLF
			PIFATQSNDFALGYPIGKLIFIFQVFKKFNFNLFR HLLVTDSYSHI*
759	102	419	MWLGQAFWAWLSFMNRWHSKFLMVRSRGEC
		11/	MI A POCKT, MY A POLININK MHOKLFINI A KOKOEC

NO: beginning nucleotide location corresponding to first amino acid residue of amino acid sequence sequence	SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
nucleotide location corresponding to first amino acid residue of amino acid sequence	•		1	
location   corresponding to first amino   corresponding to first amino acid residue of amino acid   seidue of amino acid   seidue of amino acid   sequence   corresponding	110.			
Corresponding to first amino acid residue of amino acid residue of amino acid sequence   Common acid residue of amino acid sequence   Common acid residue of amino acid sequence   Common acid residue of amino acid sequence   Common acid sequence   Com				
to first amino acid residue of amino acid of amino acid of amino acid sequence seque				
acid residue of amino acid sequence   v=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, *possible nucleotide deletion, v=possible nucleotide insertion   GAQRQLLCVFVFRDSLREGMPRRNMVSSEAHG   CLRTAVFYATYPCTSYAKETKPSACLFPLLIIG   KWMLWSFKN*				
			1	
GAQRQLLCVFVFRDSLREGMPRRNMVSSEAHG			sequence	
CLLRTAVFYATYPCTSYAKETKPSACLFPLLIIG   KWMLWSFKN*		sequence		1
KWMLWSFKN*				
760         27         371         MSSWFLRAGHGLIWVLFFRIGQAAVGVSAGPG GSPKAHLGRVASQHPHGAESSRACLLARGLPKA LSSMLAVDCRPRSGPLHRAAHIMAASLISKPVR GCLSEDDIPSPLSDSAY*           761         428         685         MGWDSKLLFLFTCLSCVTTCSVSTCFQAPLGSS SFAPSGIHGTLEFPVVRGAHKNFLPMGPMYLFP ITAGQPLTLFVKTQSAGRN*           762         293         3         MCHVHCCWKFIVELLQCVIQGIRCLYFGNICNG TCFLESCFFGMSFQGANFLFFGNSHSSFYCRR MSPFPRGEQVLHFICHSVCQCQCQCWCSGG*           763         38         385         MLLWVFLQLNYKIQAIPTYETVMTFFKSFPENC CFLDRDIGQSLRPLFLCLRLHGITKGKDXEVLR HLNFFPESWLDQVTVNHYHALENGGDMVHLK DLNTQAVRFGLLFNQENTT           764         508         1374         MLAMGALAGFWILCLLTYGYLSWGQALEEEE EGALLAQAGEKLEPSTTSTSQPHLIFILADDQGF RDVGYHGSEIKTPTLDKLAAGEGVKENYYVQP ICTPSRSQFITGKYQIHTGLQHSIIRPTQPNCLPL DNATLPQKLKEVGYSTHMVGKWHLGFYRKEC MPTRRGFDTFFGSLLGSGDYYTHYKCDSPGMC GYDLYENDNAAWDYDNGIYSTQMYTQRVQQI LASHNPTKPIFLYIAYQAVHSPLQAPGYFFEHY RSIININRRRYAAMLSCLDEAINNVTLALK           765         660         875         MRSYKPNPLIFPKLQILIFLTSYLIFTLRYLPGVF NILFKTVLLVFFLQDYSLLISANSSSFQVLSVKT YN*           766         316         456         MDLYVVIFWLVYIFSTYIITYIKGNVGLCFQILF QLSFERRPKSVR*           767         231         584         MSFPIHLRFFSLFFLHWLLLSGFSSLLPWASAFV QYSRCPEHTPSLCPGGANNPLLQAPTQMLPPLG CLLCALPASPSPYLCWHLLYHAFRNLLIPLISGA PCGSGIPKFSKCLSVS*           768         135         305         MKNLLMVHLWGICTLYLEFSAVSAISFLNHISV KTYFPNSSFYRATPMVLDFILH*           769         231         401         MLGWQIWRLRPQLLSFHTQDRCHWSITSQCSK PESQESPLS				
GSPKAHLGRVASQHPHGAESRACLLARGLPKA	560	0.2	1 221	
LSSMLAVDCRPRSOPLHRAAHIMAASLISKPVR   GCLSEDDIPSPLSDSAY*	760	21	3/1	
GCLSEDDIPSPLSDSAY*			}	
761         428         685         MGWDSKLLFLFTCLSCVTTCSVSTCFQAPLGSS SFAPSGIHGTLEFPVVRGAHKNFLPMGPMYLFP ITAGQPLTLFVKTQSAGRN*           762         293         3         MCHVHCCWKFIVELLQCVIQGIRCLYFGNICNG TCFLESCFFGMSFQGANFLFFGNSHSSSFYCRR MSPFPRGEQVLHFICHSVCQCQCQCWCSGG*           763         38         385         MLLWVFLQLNYKIQAIPTYETVMTFFKSFPENC CFLDRDIGQSLRPLFLCCLRLHGITKGKDXEVLR HLNFFPESWLDQVTVNHYHALENGGDMVHLK DLNTQAVRFGLLFNQENTT           764         508         1374         MLAMGALAGFWILCLLTYGYLSWGQALEEEE EGALLAQAGEKLEPSTTSTSQPHLIFILADDQGF RDVGYHGSEIKTPTLDKLAAEGVKLENYYVQP ICTPSRSQFITGKYQIHTGLQHSIIRPTQNCLPL DNATLPQKLKEVGYSTHMVGKWHLGFYRKEC MPTRRGFDTFFGSLLGSGDYYTHYKCDSPGMC GYDLYENDNAAWDYDNGIYSTQMYTQRVQQI LASHNPTKPIFLYIAYQAVHSPLQAPGRYFEHY RSIININRRRYAAMLSCLDEAINNVTLALK           765         660         875         MRSYKPNPLLFPKLQILIFLTSYLIFTLRYLPGVF NILFKTVLLVFFLQDYSLLISANSSSFQVLSVKT YN*           766         316         456         MDLYVVIFWLVYIFSTYIITYIKGNVGLCFQILF QLSFERRPKSVR*           767         231         584         MSFPIHLRFFSLFFLHWLLLSGFSSLLPWASAFV QYSRCPEHTPSLCPGGANNPLLQAPTQMLPPLG CLLCALPASPSPYLCWHLLLYHAFRNLLIPLISGA PCGSGIPKFSKCLSVS*           768         135         305         MKNLLMVHLWGICTLYLEFSAVSAISFLNHISV KTYPPNSSSFYRATPMVLDFILH*           769         231         401         MLGWQIWRLRPQLLSFHTQDRCHWSITSQCSK PESQESFLSTIHLLEGAQEGTPTE*           770         141         314         MRETGILLCFLSALNYITLVTSQKLILSKKMHV NHYLPKKTISKFLVFVKVFHDLVL*           771				
SFAPSGIHGTLEFPVVRGAHKNFLPMGPMYLFP				
ITAGQPLTLFVKTQSAGRN*	761	428	685	
762         293         3         MCHVHCCWKFIVELLQCVIQGIRCLYFGNICNG TCFLESCFFGMSFQGANFLFFGNSHSSSFYCRR MSPFPRGEQVLHFICHSVCQCQCQCWCSGG*           763         38         385         MLLWVFLQLNYKIQAIPTYETVMTFFKSFPENC CFLDRDIGQSLRPLFLCLRLHGITKGKDXEVLR HLNFFPESWLDQVTVNHYHALENGGDMVHLK DLNTQAVRFGLLFNQENTT           764         508         1374         MLAMGALAGFWILCLLTYGYLSWGQALEEEE EGALLAQAGEKLEPSTTSTSQPHLIFILADDQGF RDVGYHGSEIKTPTLDKLAAEGVKLENYYVQP ICTPSRSQFITGKYQIHTGLQHSIIRPTQPNCLPL DNATLPQKLKEVGYSTHMVGKWHLGFYRKEC MPTRRGFDTFFGSLLGSGDYYTHYKCDSPGMC GYDLYENDNAAWDYDNGIYSTQMYTQRVQQI LASHNPTKPIFLYIAYQAVHSPLQAPGRYFEHY RSIININRRRYAAMLSCLDEAINNVTLALK           765         660         875         MRSYKPNPLLFPKLQILIFLTSYLIFTLRYLPGVF NILFKTVLLVFFLQDYSLLISANSSFQVLSVKT YN*           766         316         456         MDLYVVIFWLVYIFSTYIITYIKGNVGLCFQILF QLSFERRPKSVR*           767         231         584         MSFPIHLRFFSLFFLHWLLLSGFSSLLPWASAFV QYSRCPEHTPSLCPGGANNPLLQAPTQMLPPLG CLLCALPASPSPYLCWHILLYHAFRNLLIPLISGA PCGSGIPKFSKCLSVS*           768         135         305         MKNLLMVHLWGICTLYLEFSAVSAISFLNHISV KTYFNSSSFYRATPMVLDFILH*           769         231         401         MLGWQIWRLRPQLLSFHTQDRCHWSITSQCSK PESQESFLSTIHLLEGAQEGTPTE*           770         141         314         MRETGILLCFLSALNYITLVTSQCCHLNSKMHV NHYLPKKTISKFLYFVKVFHDLVL*           771         55         276         MKQLIYWFSLFFCCSCCHLNRHGNRLHTTEIFP				t e e e e e e e e e e e e e e e e e e e
TCFLESCFFGMSFQGANFLFFGNSHSSSFYCRR   MSPFPRGEQVLHFICHSVCQCCQCWCSGG*				
MSPFPRGEQVLHFICHSVCQCQCQCWCSGG*	762	293	3	
763         38         385         MLLWVFLQLNYKIQAIPTYÉTVMTFFKSFPENC CFLDRDIGQSLRPLFLCLRLHGITKGKDXEVLR HLNFFPESWLDQVTVNHYHALENGGDMVHLK DLNTQAVRFGLLFNQENTT           764         508         1374         MLAMGALAGFWILCLLTYGYLSWGQALEEEE EGALLAQAGEKLEPSTTSTSQPHLIFILADDQGF RDVGYHGSEIKTPTLDKLAAEGVKLENYYVQP ICTPSRSQFITGKYQIHTGLQHSIIRPTQPNCLPL DNATLPQKLKEVGYSTHMVGKWHLGFYRKEC MPTRRGFDTFGSLLGSGDYYTHYKCDSPGMC GYDLYENDNAAWDYDNGIYSTQMYTQRVQQI LASHNPTKPIFLYIAYQAVHSPLQAPGRYFEHY RSIININRRRYAAMLSCLDEAINNVTLALK           765         660         875         MRSYKPNPLLFPKQILIFLTSYLIFTLRYLPGVF NILFKTVLVFFLQDYSLLISANSSSFQVLSVKT YN*           766         316         456         MDLYVVIFWLVYIFSTYIITYIKGNVGLCFQILF QLSFERPKSVR*           767         231         584         MSFPIHLRFFSLFFLHWLLLSGFSSLLPWASAFV QYSRCPEHTPSLCPGGANNPLLQAPTQMLPPLG CLLCALPASPSPYLCWHLLYAFRNLLIPLISGA PCGSGIPKFSKCLSVS*           768         135         305         MKNLLMVHLWGICTLYLEFSAVSAISFLNHISV KTYFPNSSSFYRATPMVLDFILH*           769         231         401         MLGWQIWRLRPQLLSFHTQDRCHWSITSQCSK PESQESFLSTIHLLEGAQEGTPTE*           770         141         314         MRETGILLCFLSALNYITLVTSQKLILSKKMHV NHYLPKKTISKFLYFVKVFHDLVL*           771         55         276         MKQLIYWFSLFFCCSCCHLNRHGNRLHTTEIFP				
CFLDRDIGQSLRPLFLCLRLHGITKGKDXEVLR				MSPFPRGEQVLHFICHSVCQCQCQCWCSGG*
HLNFFPESWLDQVTVNHYHALENGGDMVHLK	763	38	385	MLLWVFLQLNYKIQAIPTYETVMTFFKSFPENC
DLNTQAVRFGLLFNQENTT  764 508 1374 MLAMGALAGFWILCLLTYGYLSWGQALEEEE EGALLAQAGEKLEPSTTSTSQPHLIFILADDQGF RDVGYHGSEIKTPTLDKLAAEGVKLENYYVQP ICTPSRSQFITGKYQIHTGLQHSIIRPTQPNCLPL DNATLPQKLKEVGYSTHMVGKWHLGFYRKEC MPTRRGFDTFFGSLLGSGDYYTHYKCDSPGMC GYDLYENDNAAWDYDNGIYSTQMYTQRVQQI LASHNPTKPIFLYIAYQAVHSPLQAPGRYFEHY RSIININRRRYAAMLSCLDEAINNVTLALK  765 660 875 MRSYKPNPLLFPKLQILIFLTSYLIFTLRYLPGVF NILFKTVLLVFFLQDYSLLISANSSSFQVLSVKT YN*  766 316 456 MDLYVVIFWLVYIFSTYIITYIKGNVGLCFQILF QLSFERRPKSVR*  767 231 584 MSFPIHLRFFSLFFLHWLLLSGFSSLLPWASAFV QYSRCPEHTPSLCPGGANNPLLQAPTQMLPPLG CLLCALPASPSPYLCWHLLYHAFRNLLIPLISGA PCGSGIPKFSKCLSVS*  768 135 305 MKNILMVHLWGICTLYLEFSAVSAISFLNHISV KTYFPNSSSFYRATPMVLDFILH*  769 231 401 MLGWQIWRLRPQLLSFHTQDRCHWSITSQCSK PESQESFLSTIHLLEGAQEGTPTE*  770 141 314 MRETGILLCFLSALNYITLVTSQKLILSKKMHV NHYLPKKTISKFLYFVKVFHDLVL*  771 55 276 MKQLIYWFSLFFCCSCCHLNRHGNRLHTTEIFP				CFLDRDIGQSLRPLFLCLRLHGITKGKDXEVLR
Total				HLNFFPESWLDQVTVNHYHALENGGDMVHLK
EGALLAQAGEKLEPSTTSTSQPHLIFILADDQGF RDVGYHGSEIKTPTLDKLAAEGVKLENYYVQP ICTPSRSQFITGKYQIHTGLQHSIIRPTQPNCLPL DNATLPQKLKEVGYSTHMVGKWHLGFYRKEC MPTRRGFDTFFGSLLGSGDYYTHYKCDSPGMC GYDLYENDNAAWDYDNGIYSTQMYTQRVQQI LASHNPTKPIFLYIAYQAVHSPLQAPGRYFEHY RSIININRRRYAAMLSCLDEAINNVTLALK MRSYKPNPLLFPKLQILIFLTSYLIFTLRYLPGVF NILFKTVLLVFFLQDYSLLISANSSSFQVLSVKT YN*  766 316 456 MDLYVVIFWLVYIFSTYIITYIKGNVGLCFQILF QLSFERRPKSVR*  767 231 584 MSFPIHLRFFSLFFLHWLLLSGFSSLLPWASAFV QYSRCPEHTPSLCPGGANNPLLQAPTQMLPPLG CLLCALPASPSPYLCWHLLYHAFRNLLIPLISGA PCGSGIPKFSKCLSVS*  768 135 305 MKNLLMVHLWGICTLYLEFSAVSAISFLNHISV KTYFPNSSSFYRATPMVLDFILH*  769 231 401 MLGWQIWRLRPQLLSFHTQDRCHWSITSQCSK PESQESFLSTIHLLEGAQEGTPTE*  770 141 314 MRETGILLCFLSALNYITLVTSQKLILSKKMHV NHYLPKKTISKFLYFVKVFHDLVL*  771 55 276 MKQLIYWFSLFFCCSCCHLNRHGNRLHTTEIFP				DLNTQAVRFGLLFNQENTT
RDVGYHGSEIKTPTLDKLAAEGVKLENYYVQP ICTPSRSQFITGKYQIHTGLQHSIIRPTQPNCLPL DNATLPQKLKEVGYSTHMVGKWHLGFYRKEC MPTRRGFDTFFGSLLGSGDYYTHYKCDSPGMC GYDLYENDNAAWDYDNGIYSTQMYTQRVQQI LASHNPTKPIFLYIAYQAVHSPLQAPGRYFEHY RSIININRRRYAAMLSCLDEAINNVTLALK MRSYKPNPLLFPKLQILIFLTSYLIFTLRYLPGVF NILFKTVLLVFFLQDYSLLISANSSSFQVLSVKT YN*  766 316 456 MDLYVVIFWLVYIFSTYIITYIKGNVGLCFQILF QLSFERRPKSVR*  767 231 584 MSFPIHLRFFSLFFLHWLLLSGFSSLLPWASAFV QYSRCPEHTPSLCPGGANNPLLQAPTQMLPPLG CLLCALPASPSPYLCWHLLYHAFRNLLIPLISGA PCGSGIPKFSKCLSVS*  768 135 305 MKNLLMVHLWGICTLYLEFSAVSAISFLNHISV KTYFPNSSSFYRATPMVLDFILH*  769 231 401 MLGWQIWRLRPQLLSFHTQDRCHWSITSQCSK PESQESFLSTIHLLEGAQEGTPTE*  770 141 314 MRETGILLCFLSALNYITLVTSQKLILSKKMHV NHYLPKKTISKFLYFVKVFHDLVL*  771 55 276 MKQLIYWFSLFFCCSCCHLNRHGNRLHTTEIFP	764	508	1374	MLAMGALAGFWILCLLTYGYLSWGQALEEEE
RDVGYHGSEIKTPTLDKLAAEGVKLENYYVQP ICTPSRSQFITGKYQIHTGLQHSIIRPTQPNCLPL DNATLPQKLKEVGYSTHMVGKWHLGFYRKEC MPTRRGFDTFFGSLLGSGDYYTHYKCDSPGMC GYDLYENDNAAWDYDNGIYSTQMYTQRVQQI LASHNPTKPIFLYIAYQAVHSPLQAPGRYFEHY RSIININRRRYAAMLSCLDEAINNVTLALK MRSYKPNPLLFPKLQILIFLTSYLIFTLRYLPGVF NILFKTVLLVFFLQDYSLLISANSSSFQVLSVKT YN*  766 316 456 MDLYVVIFWLVYIFSTYIITYIKGNVGLCFQILF QLSFERRPKSVR*  767 231 584 MSFPIHLRFFSLFFLHWLLLSGFSSLLPWASAFV QYSRCPEHTPSLCPGGANNPLLQAPTQMLPPLG CLLCALPASPSPYLCWHLLYHAFRNLLIPLISGA PCGSGIPKFSKCLSVS*  768 135 305 MKNLLMVHLWGICTLYLEFSAVSAISFLNHISV KTYFPNSSSFYRATPMVLDFILH*  769 231 401 MLGWQIWRLRPQLLSFHTQDRCHWSITSQCSK PESQESFLSTIHLLEGAQEGTPTE*  770 141 314 MRETGILLCFLSALNYITLVTSQKLILSKKMHV NHYLPKKTISKFLYFVKVFHDLVL*  771 55 276 MKQLIYWFSLFFCCSCCHLNRHGNRLHTTEIFP				EGALLAQAGEKLEPSTTSTSQPHLIFILADDQGF
DNATLPQKLKEVGYSTHMVGKWHLGFYRKEC MPTRRGFDTFFGSLLGSGDYYTHYKCDSPGMC GYDLYENDNAAWDYDNGIYSTQMYTQRVQQI LASHNPTKPIFLYIAYQAVHSPLQAPGRYFEHY RSIININRRRYAAMLSCLDEAINNVTLALK  765 660 875 MRSYKPNPLLFPKLQILIFLTSYLIFTLRYLPGVF NILFKTVLLVFFLQDYSLLISANSSSFQVLSVKT YN*  766 316 456 MDLYVVIFWLVYIFSTYIITYIKGNVGLCFQILF QLSFERRPKSVR*  767 231 584 MSFPIHLRFFSLFFLHWLLLSGFSSLLPWASAFV QYSRCPEHTPSLCPGGANNPLLQAPTQMLPPLG CLLCALPASPSPYLCWHLLYHAFRNLLIPLISGA PCGSGIPKFSKCLSVS*  768 135 305 MKNLLMVHLWGICTLYLEFSAVSAISFLNHISV KTYFPNSSSFYRATPMVLDFILH*  769 231 401 MLGWQIWRLRPQLLSFHTQDRCHWSITSQCSK PESQESFLSTIHLLEGAQEGTPTE*  770 141 314 MRETGILLCFLSALNYITLVTSQKLILSKKMHV NHYLPKKTISKFLYFVKVFHDLVL*  771 55 276 MKQLIYWFSLFFCCSCCHLNRHGNRLHTTEIFP				RDVGYHGSEIKTPTLDKLAAEGVKLENYYVQP
DNATLPQKLKEVGYSTHMVGKWHLGFYRKEC MPTRRGFDTFFGSLLGSGDYYTHYKCDSPGMC GYDLYENDNAAWDYDNGIYSTQMYTQRVQQI LASHNPTKPIFLYIAYQAVHSPLQAPGRYFEHY RSIININRRRYAAMLSCLDEAINNVTLALK  765 660 875 MRSYKPNPLLFPKLQILIFLTSYLIFTLRYLPGVF NILFKTVLLVFFLQDYSLLISANSSSFQVLSVKT YN*  766 316 456 MDLYVVIFWLVYIFSTYIITYIKGNVGLCFQILF QLSFERRPKSVR*  767 231 584 MSFPIHLRFFSLFFLHWLLLSGFSSLLPWASAFV QYSRCPEHTPSLCPGGANNPLLQAPTQMLPPLG CLLCALPASPSPYLCWHLLYHAFRNLLIPLISGA PCGSGIPKFSKCLSVS*  768 135 305 MKNLLMVHLWGICTLYLEFSAVSAISFLNHISV KTYFPNSSSFYRATPMVLDFILH*  769 231 401 MLGWQIWRLRPQLLSFHTQDRCHWSITSQCSK PESQESFLSTIHLLEGAQEGTPTE*  770 141 314 MRETGILLCFLSALNYITLVTSQKLILSKKMHV NHYLPKKTISKFLYFVKVFHDLVL*  771 55 276 MKQLIYWFSLFFCCSCCHLNRHGNRLHTTEIFP				ICTPSRSQFITGKYQIHTGLQHSIIRPTQPNCLPL
MPTRRGFDTFFGSLLGSGDYYTHYKCDSPGMC GYDLYENDNAAWDYDNGIYSTQMYTQRVQQI LASHNPTKPIFLYIAYQAVHSPLQAPGRYFEHY RSIININRRRYAAMLSCLDEAINNVTLALK  765 660 875 MRSYKPNPLLFPKLQILIFLTSYLIFTLRYLPGVF NILFKTVLLVFFLQDYSLLISANSSSFQVLSVKT YN*  766 316 456 MDLYVVIFWLVYIFSTYIITYIKGNVGLCFQILF QLSFERRPKSVR*  767 231 584 MSFPIHLRFFSLFFLHWLLLSGFSSLLPWASAFV QYSRCPEHTPSLCPGGANNPLLQAPTQMLPPLG CLLCALPASPSPYLCWHLLYHAFRNLLIPLISGA PCGSGIPKFSKCLSVS*  768 135 305 MKNLLMVHLWGICTLYLEFSAVSAISFLNHISV KTYFPNSSSFYRATPMVLDFILH*  769 231 401 MLGWQIWRLRPQLLSFHTQDRCHWSITSQCSK PESQESFLSTIHLLEGAQEGTPTE*  770 141 314 MRETGILLCFLSALNYITLVTSQKLILSKKMHV NHYLPKKTISKFLYFVKVFHDLVL*  771 55 276 MKQLIYWFSLFFCCSCCHLNRHGNRLHTTEIFP		ĺ		
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RSIININRRRYAAMLSCLDEAINNVTLALK  765 660 875 MRSYKPNPLLFPKLQILIFLTSYLIFTLRYLPGVF NILFKTVLLVFFLQDYSLLISANSSSFQVLSVKT YN*  766 316 456 MDLYVVIFWLVYIFSTYIITYIKGNVGLCFQILF QLSFERRPKSVR*  767 231 584 MSFPIHLRFFSLFFLHWLLLSGFSSLLPWASAFV QYSRCPEHTPSLCPGGANNPLLQAPTQMLPPLG CLLCALPASPSPYLCWHLLYHAFRNLLIPLISGA PCGSGIPKFSKCLSVS*  768 135 305 MKNLLMVHLWGICTLYLEFSAVSAISFLNHISV KTYFPNSSSFYRATPMVLDFILH*  769 231 401 MLGWQIWRLRPQLLSFHTQDRCHWSITSQCSK PESQESFLSTIHLLEGAQEGTPTE*  770 141 314 MRETGILLCFLSALNYITLVTSQKLILSKKMHV NHYLPKKTISKFLYFVKVFHDLVL*  771 55 276 MKQLIYWFSLFFCCSCCHLNRHGNRLHTTEIFP				, , , , ,
765660875MRSYKPNPLLFPKLQILIFLTSYLIFTLRYLPGVF NILFKTVLLVFFLQDYSLLISANSSSFQVLSVKT YN*766316456MDLYVVIFWLVYIFSTYIITYIKGNVGLCFQILF QLSFERRPKSVR*767231584MSFPIHLRFFSLFFLHWLLLSGFSSLLPWASAFV QYSRCPEHTPSLCPGGANNPLLQAPTQMLPPLG CLLCALPASPSPYLCWHLLYHAFRNLLIPLISGA PCGSGIPKFSKCLSVS*768135305MKNLLMVHLWGICTLYLEFSAVSAISFLNHISV KTYFPNSSSFYRATPMVLDFILH*769231401MLGWQIWRLRPQLLSFHTQDRCHWSITSQCSK PESQESFLSTIHLLEGAQEGTPTE*770141314MRETGILLCFLSALNYITLVTSQKLILSKKMHV NHYLPKKTISKFLYFVKVFHDLVL*77155276MKQLIYWFSLFFCCSCCHLNRHGNRLHTTEIFP				
NILFKTVLLVFFLQDYSLLISANSSSFQVLSVKT YN*  766 316 456 MDLYVVIFWLVYIFSTYIITYIKGNVGLCFQILF QLSFERRPKSVR*  767 231 584 MSFPIHLRFFSLFFLHWLLLSGFSSLLPWASAFV QYSRCPEHTPSLCPGGANNPLLQAPTQMLPPLG CLLCALPASPSPYLCWHLLYHAFRNLLIPLISGA PCGSGIPKFSKCLSVS*  768 135 305 MKNLLMVHLWGICTLYLEFSAVSAISFLNHISV KTYFPNSSSFYRATPMVLDFILH*  769 231 401 MLGWQIWRLRPQLLSFHTQDRCHWSITSQCSK PESQESFLSTIHLLEGAQEGTPTE*  770 141 314 MRETGILLCFLSALNYITLVTSQKLILSKKMHV NHYLPKKTISKFLYFVKVFHDLVL*  771 55 276 MKQLIYWFSLFFCCSCCHLNRHGNRLHTTEIFP	765	660	875	
766 316 456 MDLYVVIFWLVYIFSTYIITYIKGNVGLCFQILF QLSFERPKSVR*  767 231 584 MSFPIHLRFFSLFFLHWLLLSGFSSLLPWASAFV QYSRCPEHTPSLCPGGANNPLLQAPTQMLPPLG CLLCALPASPSPYLCWHLLYHAFRNLLIPLISGA PCGSGIPKFSKCLSVS*  768 135 305 MKNLLMVHLWGICTLYLEFSAVSAISFLNHISV KTYFPNSSSFYRATPMVLDFILH*  769 231 401 MLGWQIWRLRPQLLSFHTQDRCHWSITSQCSK PESQESFLSTIHLLEGAQEGTPTE*  770 141 314 MRETGILLCFLSALNYITLVTSQKLILSKKMHV NHYLPKKTISKFLYFVKVFHDLVL*  771 55 276 MKQLIYWFSLFFCCSCCHLNRHGNRLHTTEIFP		000	0.0	
766316456MDLYVVIFWLVYIFSTYIITYIKGNVGLCFQILF QLSFERRPKSVR*767231584MSFPIHLRFFSLFFLHWLLLSGFSSLLPWASAFV QYSRCPEHTPSLCPGGANNPLLQAPTQMLPPLG CLLCALPASPSPYLCWHLLYHAFRNLLIPLISGA PCGSGIPKFSKCLSVS*768135305MKNLLMVHLWGICTLYLEFSAVSAISFLNHISV KTYFPNSSSFYRATPMVLDFILH*769231401MLGWQIWRLRPQLLSFHTQDRCHWSITSQCSK PESQESFLSTIHLLEGAQEGTPTE*770141314MRETGILLCFLSALNYITLVTSQKLILSKKMHV NHYLPKKTISKFLYFVKVFHDLVL*77155276MKQLIYWFSLFFCCSCCHLNRHGNRLHTTEIFP		'		
QLSFERRPKSVR*  767 231 584 MSFPIHLRFFSLFFLHWLLLSGFSSLLPWASAFV QYSRCPEHTPSLCPGGANNPLLQAPTQMLPPLG CLLCALPASPSPYLCWHLLYHAFRNLLIPLISGA PCGSGIPKFSKCLSVS*  768 135 305 MKNLLMVHLWGICTLYLEFSAVSAISFLNHISV KTYFPNSSSFYRATPMVLDFILH*  769 231 401 MLGWQIWRLRPQLLSFHTQDRCHWSITSQCSK PESQESFLSTIHLLEGAQEGTPTE*  770 141 314 MRETGILLCFLSALNYITLVTSQKLILSKKMHV NHYLPKKTISKFLYFVKVFHDLVL*  771 55 276 MKQLIYWFSLFFCCSCCHLNRHGNRLHTTEIFP	766	316	456	
767231584MSFPIHLRFFSLFFLHWLLLSGFSSLLPWASAFV QYSRCPEHTPSLCPGGANNPLLQAPTQMLPPLG CLLCALPASPSPYLCWHLLYHAFRNLLIPLISGA PCGSGIPKFSKCLSVS*768135305MKNLLMVHLWGICTLYLEFSAVSAISFLNHISV KTYFPNSSSFYRATPMVLDFILH*769231401MLGWQIWRLRPQLLSFHTQDRCHWSITSQCSK PESQESFLSTIHLLEGAQEGTPTE*770141314MRETGILLCFLSALNYITLVTSQKLILSKKMHV NHYLPKKTISKFLYFVKVFHDLVL*77155276MKQLIYWFSLFFCCSCCHLNRHGNRLHTTEIFP	700	310	1430	
QYSRCPEHTPSLCPGGANNPLLQAPTQMLPPLG CLLCALPASPSPYLCWHLLYHAFRNLLIPLISGA PCGSGIPKFSKCLSVS*  768 135 305 MKNLLMVHLWGICTLYLEFSAVSAISFLNHISV KTYFPNSSSFYRATPMVLDFILH*  769 231 401 MLGWQIWRLRPQLLSFHTQDRCHWSITSQCSK PESQESFLSTIHLLEGAQEGTPTE*  770 141 314 MRETGILLCFLSALNYITLVTSQKLILSKKMHV NHYLPKKTISKFLYFVKVFHDLVL*  771 55 276 MKQLIYWFSLFFCCSCCHLNRHGNRLHTTEIFP	767	221	501	
CLLCALPASPSPYLCWHLLYHAFRNLLIPLISGA PCGSGIPKFSKCLSVS*  768 135 305 MKNLLMVHLWGICTLYLEFSAVSAISFLNHISV KTYFPNSSSFYRATPMVLDFILH*  769 231 401 MLGWQIWRLRPQLLSFHTQDRCHWSITSQCSK PESQESFLSTIHLLEGAQEGTPTE*  770 141 314 MRETGILLCFLSALNYITLVTSQKLILSKKMHV NHYLPKKTISKFLYFVKVFHDLVL*  771 55 276 MKQLIYWFSLFFCCSCCHLNRHGNRLHTTEIFP	707	231	304	1
PCGSGIPKFSKCLSVS*  768 135 305 MKNLLMVHLWGICTLYLEFSAVSAISFLNHISV KTYFPNSSSFYRATPMVLDFILH*  769 231 401 MLGWQIWRLRPQLLSFHTQDRCHWSITSQCSK PESQESFLSTIHLLEGAQEGTPTE*  770 141 314 MRETGILLCFLSALNYITLVTSQKLILSKKMHV NHYLPKKTISKFLYFVKVFHDLVL*  771 55 276 MKQLIYWFSLFFCCSCCHLNRHGNRLHTTEIFP				
768135305MKNLLMVHLWGICTLYLEFSAVSAISFLNHISV KTYFPNSSSFYRATPMVLDFILH*769231401MLGWQIWRLRPQLLSFHTQDRCHWSITSQCSK PESQESFLSTIHLLEGAQEGTPTE*770141314MRETGILLCFLSALNYITLVTSQKLILSKKMHV NHYLPKKTISKFLYFVKVFHDLVL*77155276MKQLIYWFSLFFCCSCCHLNRHGNRLHTTEIFP				
KTYFPNSSFYRATPMVLDFILH*  769 231 401 MLGWQIWRLRPQLLSFHTQDRCHWSITSQCSK PESQESFLSTIHLLEGAQEGTPTE*  770 141 314 MRETGILLCFLSALNYITLVTSQKLILSKKMHV NHYLPKKTISKFLYFVKVFHDLVL*  771 55 276 MKQLIYWFSLFFCCSCCHLNRHGNRLHTTEIFP	760	125	205	. <u>.                                   </u>
769231401MLGWQIWRLRPQLLSFHTQDRCHWSITSQCSK PESQESFLSTIHLLEGAQEGTPTE*770141314MRETGILLCFLSALNYITLVTSQKLILSKKMHV NHYLPKKTISKFLYFVKVFHDLVL*77155276MKQLIYWFSLFFCCSCCHLNRHGNRLHTTEIFP	/00	133	303	
PESQESFLSTIHLLEGAQEGTPTE*  770 141 314 MRETGILLCFLSALNYITLVTSQKLILSKKMHV NHYLPKKTISKFLYFVKVFHDLVL*  771 55 276 MKQLIYWFSLFFCCSCCHLNRHGNRLHTTEIFP	7(0	221	401	
770 141 314 MRETGILLCFLSALNYITLVTSQKLILSKKMHV NHYLPKKTISKFLYFVKVFHDLVL* 771 55 276 MKQLIYWFSLFFCCSCCHLNRHGNRLHTTEIFP	/69	231	401	
NHYLPKKTISKFLYFVKVFHDLVL* 771 55 276 MKQLIYWFSLFFCCSCCHLNRHGNRLHTTEIFP				
771 55 276 MKQLIYWFSLFFCCSCCHLNRHGNRLHTTEIFP	770	141	314	
	771	55	276	
SLFHLVCCADPLPWMPAHSFGSPFWSLFSTYPG			<u> </u>	SLFHLVCCADPLPWMPAHSFGSPFWSLFSTYPG

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	
	acid residue	amino acid	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
		1	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
ļ	sequence		deletion, \=possible nucleotide insertion
770	120	254	RNSRGCQ*
772	139	354	MLLFSLNFFFWKIVMFHKNVIFILTCNGFIIVTF
			KWIDKFILNISILISNTVNVNSHNPHKQKFFGDL
			SNF*
773	269	457	MQLKFSQLTTSSLSFSSALWLLAFSRVFLLADS
			NLFVKPSSDLGSDTCSADFCDFRKLSFFR*
774	96	1385	MCPGALWVALPLLSLLAGSLQGKPLQSWGRGS
	-		AGGNAHSPLGVPGGGLPEHTFNLKMFLENVKV
	1		DFLRSLNLSGVPSQDKTRVEPPQYMIDLYNRYT
			SDKSTTPASNIVRSFSMEDAISITATEDFPFQKHI
			LLFNISIPRHEQITRAELRLYVSCQNHVDPSHDL
			KGSVVIYDVLDGTDAWDSATETKTFLVSQDIQ
			DEGWETLEVSSAVKRWVRSDSTKSKNKLEVT
			VESHRKGCDTLDISVPPGSRNLPFFVVFSNDHSS
			GTKETRLELREMISHEQESVLKKLSKDGSTEAG
			ESSHEEDTDGHVAAGSTLARRKRSAGAGSHCO
			KTSLRVNFEDIGWDSWIIAPKEYEAYECKGGCF
			FPLADDVTPTKHAIVQTLVHLKFPTKVGKACC
			VPTKLSPISVLYKDDMGVPTLKYHYEGMSVAE
			CGCR*
775	187	354	MFGMIKRRVRRAVFVGRTVLCGSCNSGIIMHR
			GKTPPLKMVCRFEESFSCLFLNS*
776	22	168	MGFLFLLDSALMQTWVTVIDVSLHHVEIKAPRI
		100	RLMWSLPLRRQKYTM*
777	37	357	MLATLACMAIPWTHLGCSCLLACLPFSHHLGL
' ' '	3,	337	SEDIESEK DENTAL EKH OHEGUDI GUNGA POET
			SEDIISSEKPSVTMLSKILQHFSHPLSHYSAFSET
		_	LVLPETYLFTCLASFLPHYHVSFLRVRDLVRDN HCILRV*
778	85	225	
770		223	MHTPHLPNIIVYFILLYICSQYLYLLTIRHNHLT QSLFYNKLLSVL*
779	187	396	
119	107	390	MPVTPDPSAVSLFVTPWPLLLCLPWPHRVPGQS
			HPGLHSRAPVHRLKPGPPARLQLPAAHRNLRH
780	9	210	LSIF*
/00	7	218	MSWYTCQCLFFLSNTLRNGATSCHWYCSPDD
			MQMVDFSSTYERIFRPFVFKIKGPDSFRIDMSPI
701	200	100	PEDI*
781	398	192	MARSARTFLLSSTWHLTKFPMSAGYFSPCSWL
	İ		AAVIRLIQRVLMFFFFRYRALVHFTKARITVLT
		· · · · · · · · · · · · · · · · · · ·	ANL*
782	216	791	MAGPELLLDSNIRLWVVLPIVIITFFVGMIRHYV
			SILLQSDKKLTQEQVSDSQVLIRSRVLRENGKYI
			PKQSFLTRKYYFNNPEDGFFKKTKRKVVPPSP
			MTDPTMLTDMMKGNVTNVLPMILIGGWINMT
			The state of the s

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location corresponding to first amino acid residue of amino acid sequence    Record	<b>)</b> _
corresponding to first amino acid residue of amino acid residue of amino acid sequence    M=Methionine, N=Asparagine, P=Proline, Q=Glutamine, R=Arginine, S=Serine, T=Threo V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide deletion, \=possible nucleotide insertion   FSGFVTTKVPFPLTLRFKPMLQQGIELLTLI WVSSASLGTSPMVFGLRSIYSSDSGPR*	
to first amino acid residue of amino acid residue of amino acid sequence  sequence    V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotid eletion, \=possible nucleotide insertion   FSGFVTTKVPFPLTLRFKPMLQQGIELLTLI WVSSASLGTSPMVFGLRSIYSSDSGPR*	,
acid residue of amino acid sequence    V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide leletion, \=possible nucleotide insertion   FSGFVTTKVPFPLTLRFKPMLQQGIELLTLI WVSSASLGTSPMVFGLRSIYSSDSGPR*	nine
of amino acid sequence    X=Unknown, *=Stop codon, /=possible nucleot deletion, \=possible nucleotide insertion   FSGFVTTKVPFPLTLRFKPMLQQGIELLTLI WVSSASLGTSPMVFGLRSIYSSDSGPR*     783   285   440   MLFVVLPLLIIVFNIPMREAVFDFLFMIKIIK VFYCIACFIIKQALVF*     784   277   471   MVTYFIKCFHYEVSFLLWFAVVRNDVDRF SLFSSYSLFSTYPDTCPLFKLPTHLLCCLEE     785   256   429   MAVPIMLFYFSLLYKSLAFFESYSFAEYHP RQGCVKDILKRLIWFLIHLHLDAG     786   412   672   MAVKNVALVITWAYGFVKVTLSLLVFCV YVILHLRMYITHKGACRHMSASWLATNCI WGCHSTFHLEIENNNTIILLELCA*     787   778   975   MFGVSGFCLLFTFLELVLLGLGRWWRTWF SSSSKYFLTSESTRRHKKATDSLPVVETKEE     EA	,
sequence   deletion, \=possible nucleotide insertion	ide
FSGFVTTKVPFPLTLRFKPMLQQGIELLTLI WVSSASLGTSPMVFGLRSIYSSDSGPR*  783 285 440 MLFVVLPLLIIVFNIPMREAVFDFLFMIKIIK VFYCIACFIIKQALVF*  784 277 471 MVTYFIKCFHYEVSFLLWFAVVRNDVDRF SLFSSYSLFSTYPDTCPLFKLPTHLLCCLEE  785 256 429 MAVPIMLFYFSLLYKSLAFFESYSFAEYHP RQGCVKDILKRLIWFLIHLHLDAG  786 412 672 MAVKNVALVITWAYGFVKVTLSLLVFCV YVILHLRMYITHKGACRHMSASWLATNCI WGCHSTFHLEIENNNTIILLELCA*  787 778 975 MFGVSGFCLLFTFLELVLLGLGRWWRTWI SSSSKYFLTSESTRRHKKATDSLPVVETKE EA  788 15 1334 MAAARCWRPLLRGPRLSLHTAANAAATA TCQDVAATPVARYPPIVASMTADSKAARL RWQATVHAAESVDEKLRILTKMQFMKYM QTFALNADRWYQYFTKTVFLSGLPPPPAEI PEPEPEPALDLAALRAVACDCLLQEHFYLE RVHRYEESEVISLPFLDQLVSTLVGLLSPHN AAAALDYRCPVHFYWVRGEEIIPRGHRRG DLRYQIDDKPNNQIRISKQLAEFVPLDYSVI TIKCKPDKLPLFKRQYENHIFVGSKTADPCI HTQFHLLPDKLRRERLLRQNCADQIEVVFF AIASLFAWTGAQAMYQGFWSEADVTRPFV AVITDGKYFSFFCYQLNTLALTTQADQNNI NICWGTQSKPLYETIEDNDVKGFNDDVLLC	luc
WVSSASLGTSPMVFGLRSIYSSDSGPR*   783   285	) A C
783       285       440       MLFVVLPLLIIVFNIPMREAVFDFLFMIKIIK VFYCIACFIIKQALVF*         784       277       471       MVTYFIKCFHYEVSFLLWFAVVRNDVDRF SLFSSYSLFSTYPDTCPLFKLPTHLLCCLEE.         785       256       429       MAVPIMLFYFSLLYKSLAFFESYSFAEYHP RQGCVKDILKRLIWFLIHLHLDAG         786       412       672       MAVKNVALVITWAYGFVKVTLSLLVFCV YVILHLRMYITHKGACRHMSASWLATNCI WGCHSTFHLEIENNNTIILLELCA*         787       778       975       MFGVSGFCLLFTFLELVLGLGRWWRTWF SSSSKYFLTSESTRHKKATDSLPVVETKEE EA         788       15       1334       MAAARCWRPLLRGPRLSLHTAANAAATATCQDVAATPVARYPPIVASMTADSKAARLRWQATVHAAESVDEKLRILTKMQFMKYMQTFALNADRWYQYFTKTVFLSGLPPPPAEIPEPEPEPALDLAALRAVACDCLLQEHFYLRRVHYEESEVISLPFLDQLVSTLVGLLSPHNAAAALDYRCPVHFYWRGEEIIPRGHRRGDLRYQIDDKPNNQIRISKQLAEFVPLDYSVTIKCKPDKLPLFKRQYENHIFVGSKTADPCHTQFHLPDKLRRERLLRQNCADQIEVVFRAIASLFAWTGAQAMYQGFWSEADVTRPFVAVITDGKYFSFCYQLNTLALTTQADQNNINICWGTQSKPLYETIEDNDVKGFNDDVLLQ	AG
784       277       471       MVTYFIKCFHYEVSFLLWFAVVRNDVDRF SLFSSYSLFSTYPDTCPLFKLPTHLLCCLEE         785       256       429       MAVPIMLFYFSLLYKSLAFFESYSFAEYHP RQGCVKDILKRLIWFLIHLHLDAG         786       412       672       MAVKNVALVITWAYGFVKVTLSLLVFCV YVILHLRMYITHKGACRHMSASWLATNCI WGCHSTFHLEIENNNTIILLELCA*         787       778       975       MFGVSGFCLLFTFLELVLLGLGRWWRTWF SSSSKYFLTSESTRHKKATDSLPVVETKEGEA         788       15       1334       MAAARCWRPLLRGPRLSLHTAANAAATA' TCQDVAATPVARYPPIVASMTADSKAARL RWQATVHAAESVDEKLRILTKMQFMKYM QTFALNADRWYQFTKTVFLSGLPPPPAEI PEPEPALDLAALRAVACDCLLQEHFYLE RVHRYEESEVISLPFLDQLVSTLVGLLSPHN AAAALDYRCPVHFYWVRGEEIIPRGHRRG DLRYQIDDKPNNQIRISKQLAEFVPLDYSVITIKCKPDKLPLFKRQYENHIFVGSKTADPC'HTQFHLLPDKLRRERLLRQNCADQIEVVFF AAAALDYRCPVHFYWVRGEEIIPRGHRRG DLRYQIDDKPNNQIRISKQLAEFVPLDYSVITIKCKPDKLPLFKRQYENHIFVGSKTADPC'HTQFHLLPDKLRRERLLRQNCADQIEVVFF AIASLFAWTGAQAMYQGFWSEADVTRPFV AVITDGKYFSFFCYQLNTLALTTQADQNNINICWGTQSKPLYETIEDNDVKGFNDDVLLOCK	VLK
SLFSSYSLFSTYPDTCPLFKLPTHLLCCLEE  785 256 429 MAVPIMLFYFSLLYKSLAFFESYSFAEYHP RQGCVKDILKRLIWFLIHLHILDAG  786 412 672 MAVKNVALVITWAYGFVKVTLSLLVFCV YVILHLRMYITHKGACRHMSASWLATNCI WGCHSTFHLEIENNNTIILLELCA*  787 778 975 MFGVSGFCLLFTFLELVLLGLGRWWRTWI SSSSKYFLTSESTRRHKKATDSLPVVETKE EA  788 15 1334 MAAARCWRPLLRGPRLSLHTAANAAATA' TCQDVAATPVARYPPIVASMTADSKAARL RWQATVHAAESVDEKLRILTKMQFMKYM QTFALNADRWYQYFTKTVFLSGLPPPPAEI PEPEPEPALDLAALRAVACDCLLQEHFYLR RVHRYEESEVISLPFLDQLVSTLVGLLSPHN AAAALDYRCPVHFYWVRGEEIIPRGHRRG DLRYQIDDKPNQIRISKQLAEFVPLDYSVI TIKCKPDKLPLFKRQYENHIFVGSKTADPCHTQFHLLPDKLRRERLLRQNCADQIEVVFF AIASLFAWTGAQAMYQGFWSEADVTRPFV AVITDGKYFSFFCYQLNTLALTTQADQNNI NICWGTQSKPLYETIEDNDVKGFNDDVLLO	
785 256 429 MAVPIMLFYFSLLYKSLAFFESYSFAEYHP RQGCVKDILKRLIWFLIHLHLDAG 786 412 672 MAVKNVALVITWAYGFVKVTLSLLVFCV YVILHLRMYITHKGACRHMSASWLATNCI WGCHSTFHLEIENNNTIILLELCA* 787 778 975 MFGVSGFCLLFTFLELVLLGLGRWWRTWI SSSSKYFLTSESTRRHKKATDSLPVVETKE EA 788 15 1334 MAAARCWRPLLRGPRLSLHTAANAAATA TCQDVAATPVARYPPIVASMTADSKAARL RWQATVHAAESVDEKLRILTKMQFMKYM QTFALNADRWYQYFTKTVFLSGLPPPPAEI PEPEPEPALDLAALRAVACDCLLQEHFYLR RVHRYEESEVISLPFLDQLVSTLVGLLSPHN AAAALDYRCPVHFYWVRGEEIIPRGHRRG DLRYQIDDKPNNQIRISKQLAEFVPLDYSVI TIKCKPDKLPLFKRQYENHIFVGSKTADPC HTQFHLLPDKLRRERLLRQNCADQIEVVFR AIASLFAWTGAQAMYQGFWSEADVTRPFV AVITDGKYFSFFCYQLNTLALTTQADQNNI NICWGTQSKPLYETIEDNDVKGFNDDVLLC	VSL
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786 412 672 MAVKNVALVITWAYGFVKVTLSLLVFCV YVILHLRMYITHKGACRHMSASWLATNCI WGCHSTFHLEIENNNTIILLELCA*  787 778 975 MFGVSGFCLLFTFLELVLLGLGRWWRTWI SSSSKYFLTSESTRRHKKATDSLPVVETKE EA  788 15 1334 MAAARCWRPLLRGPRLSLHTAANAAATA TCQDVAATPVARYPPIVASMTADSKAARL RWQATVHAAESVDEKLRILTKMQFMKYM QTFALNADRWYQYFTKTVFLSGLPPPPAEI PEPEPEPALDLAALRAVACDCLLQEHFYLR RVHRYEESEVISLPFLDQLVSTLVGLLSPHN AAAALDYRCPVHFYWVRGEEIIPRGHRRG DLRYQIDDKPNNQIRISKQLAEFVPLDYSVI TIKCKPDKLPLFKRQYENHIFVGSKTADPCH HTQFHLLPDKLRRERLLRQNCADQIEVVFR AIASLFAWTGAQAMYQGFWSEADVTRPFV AVITDGKYFSFFCYQLNTLALTTQADQNNI NICWGTQSKPLYETIEDNDVKGFNDDVLLO	PTSG
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SSSSKYFLTSESTRRHKKATDSLPVVETKEGEA  788 15 1334 MAAARCWRPLLRGPRLSLHTAANAAATATCQDVAATPVARYPPIVASMTADSKAARLRWQATVHAAESVDEKLRILTKMQFMKYMQTFALNADRWYQYFTKTVFLSGLPPPPAEIPEPEPALDLAALRAVACDCLLQEHFYLRRVHRYEESEVISLPFLDQLVSTLVGLLSPHNAAAALDYRCPVHFYWVRGEEIIPRGHRRGDLRYQIDDKPNNQIRISKQLAEFVPLDYSVITIKCKPDKLPLFKRQYENHIFVGSKTADPCHTQFHLLPDKLRRERLLRQNCADQIEVVFRAIASLFAWTGAQAMYQGFWSEADVTRPFVAVITDGKYFSFFCYQLNTLALTTQADQNNINICWGTQSKPLYETIEDNDVKGFNDDVLLO	
EA  788  15  1334  MAAARCWRPLLRGPRLSLHTAANAAATA TCQDVAATPVARYPPIVASMTADSKAARL RWQATVHAAESVDEKLRILTKMQFMKYM QTFALNADRWYQYFTKTVFLSGLPPPPAEI PEPEPEPALDLAALRAVACDCLLQEHFYLR RVHRYEESEVISLPFLDQLVSTLVGLLSPHN AAAALDYRCPVHFYWVRGEEIIPRGHRRG DLRYQIDDKPNNQIRISKQLAEFVPLDYSVI TIKCKPDKLPLFKRQYENHIFVGSKTADPCI HTQFHLLPDKLRRERLLRQNCADQIEVVFR AIASLFAWTGAQAMYQGFWSEADVTRPFV AVITDGKYFSFFCYQLNTLALTTQADQNNI NICWGTQSKPLYETIEDNDVKGFNDDVLLO	CHK
788 15 1334 MAAARCWRPLLRGPRLSLHTAANAAATA' TCQDVAATPVARYPPIVASMTADSKAARL RWQATVHAAESVDEKLRILTKMQFMKYM QTFALNADRWYQYFTKTVFLSGLPPPPAEI PEPEPEPALDLAALRAVACDCLLQEHFYLR RVHRYEESEVISLPFLDQLVSTLVGLLSPHN AAAALDYRCPVHFYWVRGEEIIPRGHRRG DLRYQIDDKPNNQIRISKQLAEFVPLDYSVI TIKCKPDKLPLFKRQYENHIFVGSKTADPCI HTQFHLLPDKLRRERLLRQNCADQIEVVFR AIASLFAWTGAQAMYQGFWSEADVTRPFV AVITDGKYFSFFCYQLNTLALTTQADQNNI NICWGTQSKPLYETIEDNDVKGFNDDVLLO	QFQ
TCQDVAATPVARYPPIVASMTADSKAARL RWQATVHAAESVDEKLRILTKMQFMKYM QTFALNADRWYQYFTKTVFLSGLPPPPAEI PEPEPEPALDLAALRAVACDCLLQEHFYLF RVHRYEESEVISLPFLDQLVSTLVGLLSPHN AAAALDYRCPVHFYWVRGEEIIPRGHRRG DLRYQIDDKPNNQIRISKQLAEFVPLDYSVI TIKCKPDKLPLFKRQYENHIFVGSKTADPCI HTQFHLLPDKLRRERLLRQNCADQIEVVFF AIASLFAWTGAQAMYQGFWSEADVTRPFV AVITDGKYFSFFCYQLNTLALTTQADQNNI NICWGTQSKPLYETIEDNDVKGFNDDVLLO	
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RWQATVHAAESVDEKLRILTKMQFMKYM QTFALNADRWYQYFTKTVFLSGLPPPPAEI PEPEPEPALDLAALRAVACDCLLQEHFYLR RVHRYEESEVISLPFLDQLVSTLVGLLSPHN AAAALDYRCPVHFYWVRGEEIIPRGHRRG DLRYQIDDKPNNQIRISKQLAEFVPLDYSVI TIKCKPDKLPLFKRQYENHIFVGSKTADPCI HTQFHLLPDKLRRERLLRQNCADQIEVVFR AIASLFAWTGAQAMYQGFWSEADVTRPFV AVITDGKYFSFFCYQLNTLALTTQADQNNI NICWGTQSKPLYETIEDNDVKGFNDDVLLO	RRIE
PEPEPALDLAALRAVACDCLLQEHFYLE RVHRYEESEVISLPFLDQLVSTLVGLLSPHN AAAALDYRCPVHFYWVRGEEIIPRGHRRG DLRYQIDDKPNNQIRISKQLAEFVPLDYSVI TIKCKPDKLPLFKRQYENHIFVGSKTADPCI HTQFHLLPDKLRRERLLRQNCADQIEVVFF AIASLFAWTGAQAMYQGFWSEADVTRPFV AVITDGKYFSFFCYQLNTLALTTQADQNNI NICWGTQSKPLYETIEDNDVKGFNDDVLLO	
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TIKCKPDKLPLFKRQYENHIFVGSKTADPC HTQFHLLPDKLRRERLLRQNCADQIEVVFF AIASLFAWTGAQAMYQGFWSEADVTRPFV AVITDGKYFSFFCYQLNTLALTTQADQNNI NICWGTQSKPLYETIEDNDVKGFNDDVLLQ	RID
TIKCKPDKLPLFKRQYENHIFVGSKTADPCE HTQFHLLPDKLRRERLLRQNCADQIEVVFF AIASLFAWTGAQAMYQGFWSEADVTRPFV AVITDGKYFSFFCYQLNTLALTTQADQNNI NICWGTQSKPLYETIEDNDVKGFNDDVLLG	PIEIP
AIASLFAWTGAQAMYQGFWSEADVTRPFV AVITDGKYFSFFCYQLNTLALTTQADQNNI NICWGTQSKPLYETIEDNDVKGFNDDVLLQ	
AVITDGKYFSFFCYQLNTLALTTQADQNNI NICWGTQSKPLYETIEDNDVKGFNDDVLLQ	AN
NICWGTQSKPLYETIEDNDVKGFNDDVLLQ	'SQ
NICWGTQSKPLYETIEDNDVKGFNDDVLLQ	PRK
L	
789 680 880 MGLFAIHISSWLLRACFLIIENFESVLYISNT	HPFI
YMGLHRFFSQPSVWILLFLTGPLNTKSYYH	
790 85 315 MFKVVFCFGLVWFCFQRAHKPIRFEKHNF	
GNLFSMNIPIVTIRSHHRTSCYHKLITCEQQ'	
TNIKRHSKL*	
791 112 273 MNLYLFAVLFFYVFLHIKIIFICFATKWHNL	FSK
FSYFCILHVKALSLNLGSG*	
792 142 297 MYSLSLQLPVLCVLKSFKAYSLLWGVSTG	<b>VKE</b>
GFAGRTIVNHESYYLRIVW*	
793 127 315 MCTLFMHLLFCHLQSIQLKQELRLNYLTLT	QF
WQRCYSEMIFFCLSKVFLHVFQDGLEHHLE	*
794 1401 1553 MFATTLGVMGLWSGIIICTVFQAVCFLGFII	
WKKACQQGALKTLKEF*	
795 181 390 MHLTLSLLLFSLHFPTYIIRVNFCLVSNLFQI	RMR
STKLLRLIDLDFSFTFSLLDLPPVNEYDMYII	

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
110.	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
			V=Valine, W=Tryptophan, Y=Tyrosine,
	acid residue	amino acid	
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence		deletion, \=possible nucleotide insertion
706	040	1222	GK NOWEYHEL SERVOCKILL A H. EMCCALDIMINE A D.V.
796	849	1322	MVKSVIFLSFWQGMLLAÏLEKCGAIPKIHSARV
			SVGEGTVAAGYQDFIICGEMFFAALALRHAFT
			YKVYADKRLDAQGRCAPMKSISSSLKETMNPH
			DIVQDAIHNFSPAYQQYTQQSTLEPGPTWRGG
			AHGLSRSHSLSGARDNEKTLLLSSDDEF*
797	80	271	MGKKVTLLLQKCAWLLLVCCLFTGIKYLNKCF
			ITDRELLRDVHNALNILRHNFYVNWASLNTF*
798	249	518	MVQLFIPILKFQLGYSVLSLCNHVLEFLFPSSLS
			GIFSSSLPLLLPFPLSLPSLPPSLFPSLRVLLCHPH
			WSVASNSWAVAILLPQPPE*
799	481	651	MYLLILLSTKFSCISSLPGLDYRQDSMLCQGISL
			APTLLIIHLFMCIMIKYKPLIR*
800	148	288	MCVHPYVCTCACMHVCVCLCAWCLSQPGGLG
			GFSEEVTSLPRPRAL*
801	154	510	MLFLKKIQFLKCNKVFRSLDFCVALPLLFSSSA
			VLQITPVDTFSDPHLVLTLVKLLMNILNIAVISL
			TFPGEYEVSLAFENILMYTHAFIICFCNRQWLFK
			SNSESNLSSNVNLFDSC*
802	99	434	MQLHGKGSQDPSTKGHIKALQTVTSFLLLCAIY
			FLSMIISVCNFGRLEKQPVFMFCQAIIFSYPSTHP
			FILILGNKKLKQIFLSVLRHVRYWVKDRSLRLH
			RFTRGALCVF*
803	1189	233	MAPWAEAEHSALNPLRAVWLTLTAAFLLTLLL
1			QLLPPGLLPGCAIFQDLIRYGKTKCGEPSRPAAC
			RAFDVPKRYFSHFYIISVLWNGFLLWCLTQSLF
			LGAPFPSWLHGLLRILGAAOFOGGELALSAFLV
			LVFLWLHSLRRLFECLYVSVFSNVMIHVVQYC
			FGLVYYVLVGLTVLSQVPMDGRNAYITGKNLL
			MQARWFHILGMMMFIWSSAHQYKCHVILGNL
		Í	RKNKAGVVIHCNHRIPFGDWFEYVSSPNYLAE
			LMIYVSMAVTFGFHNLTWWLVVTNVFFNQAL
	1		SAFLSHQFYKSKFVSYPKHRKAFLPFLF*
804	92	1246	MEFGLSWLFLVAILKGVQCEVQLVESGGGLVQ
004	12	1240	PGGSLRLSCAASGFTFSSYAMSWVRQAPGKGL
			EWVSGLSGSGGSSTYYADSVKGRFTISRDNSK
	1		GTLYLQMNSLRADDTARYYCAKGGVELASTK
1	1		PSSIWRLNPIRYWYFDLWGQGTLVTVSSGDGSS
1			GGSGGASTGEIVLTQSPGTLSLSPGERATLSCRA
			SQSVSSSYLAWYQQKPGQAPRLLIYGASSRAT
			GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQ
			YGSSPTTFGQGTKVDIKRTVAAPSVFIFPPSDEQ
			LKSGTASVVCLLNNFYPREAKVQWKVDNALQ

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence	sequence	deletion, \=possible nucleotide insertion
	Sequence		SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK
			HKVYACEVTHQGLSSPVTKSFNRGEC*
805	92	1246	MEFGLSWLFLVAILKGVQCEVQLVESGGGLVQ
003	12	1240	PGGSLRLSCAASGFTFSSYAMSWVRQAPGKGL
			EWVSGLSGSGGSSTYYADSVKGRFTISRDNSK
			GTLYLOMNSLRADDTARYYCAKGGVELASTK
			PSSIWRLNPIRYWYFDLWGQGTLVTVSSGDGSS
			GGSGGASTGEIVLTQSPGTLSLSPGERATLSCRA
	1		SQSVSSSYLAWYQQKPGQAPRLLIYGASSRAT
			GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQ
		1	YGSSPTTFGQGTKVDIKRTVAAPSVFIFPPSDEQ
			LKSGTASVVCLLNNFYPREAKVQWKVDNALQ
			SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK
			HKVYACEVTHQGLSSPVTKSFNRGEC*
806	92	1246	MEFGLSWLFLVAILKGVQCEVQLVESGGGLVQ
800	92	1240	PGGSLRLSCAASGFTFSSYAMSWVRQAPGKGL
			EWVSGLSGSGGSSTYYADSVKGRFTISRDNSK
			GTLYLQMNSLRADDTARYYCAKGGVELASTK
			PSSIWRLNPIRYWYFDLWGQGTLVTVSSGDGSS
			GGSGGASTGEIVLTQSPGTLSLSPGERATLSCRA
			SQSVSSSYLAWYQQKPGQAPRLLIYGASSRAT
			GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQ
			YGSSPTTFGQGTKVDIKRTVAAPSVFIFPPSDEQ
			LKSGTASVVCLLNNFYPREAKVQWKVDNALQ
·			SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK
007	00	1046	HKVYACEVTHQGLSSPVTKSFNRGEC*
807	92	1246	MEFGLSWLFLVAILKGVQCEVQLVESGGGLVQ
			PGGSLRLSCAASGFTFSSYAMSWVRQAPGKGL
			EWVSGLSGSGGSSTYYADSVKGRFTISRDNSK
			GTLYLQMNSLRADDTARYYCAKGGVELASTK
			PSSIWRLNPIRYWYFDLWGQGTLVTVSSGDGSS
			GGSGGASTGEIVLTQSPGTLSLSPGERATLSCRA
			SQSVSSSYLAWYQQKPGQAPRLLIYGASSRAT
			GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQ
			YGSSPTTFGQGTKVDIKRTVAAPSVFIFPPSDEQ
			LKSGTASVVCLLNNFYPREAKVQWKVDNALQ
			SGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK
			HKVYACEVTHQGLSSPVTKSFNRGEC*
808	63	203	MFPPYFSLILLLFTFASKFFLSLNLKKSNIVKARI
			ESTKTVISKRC*
809	157	387	MQSVIRKQFTALAGFCFWFCLFTLAVLSLTLLI
			CKLRIMPFKLEGLFQELNKSWHMKLLSQDRELI
			NMLLLLMGRS*
	<del></del>	· · · · · · · · · · · · · · · · · · ·	<u> </u>

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence	sequence	deletion, \=possible nucleotide insertion
810	50	3616	MDLPRGLVVAWALSLWPGFTDTFNMDTRKPR
810	30	2010	1
			VIPGSRTAFFGYTVQQHDISGNKWLVVGAPLET
			NGYQKTGDVYKCPVIHGNCTKLNLGRVTLSNV
			SERKDNMRLGLSLATNPKDNSFLACSPLWSHE
			CGSSYYTTGMCSRVNSNFRFSKTVAPALQRCQ
			TYMDIVIVLDGSNSIYPWVEVQHFLINILKKFYI
			GPGQIQVGVVQYGEDVVHEFHLNDYRSVKDV
			VEAASHIEQRGGTETRTAFGIEFARSEAFQKGG
			RKGAKKVMIVITDGESHDSPDLEKVIQQSERDN
			VTRYAVAVLGYYNRRGINPETFLNEIKYIASDP
	:		DDKHFFNVTDEAALKDIVDALGDRIFSLEGTNK
		Į	NETSFGLEMSQTGFSSHVVEDGVLLGAVGAYD
			WNGAVLKETSAGKVIPLRESYLKEFPEELKNH
			GAYLGYTVTSVVSSRQGRVYVAGAPRFNHTG
			KVILFTMHNNRSLTIHQAMRGQQIGSYFGSEITS
			VDIDGDGVTDVLLVGAPMYFNEGRERGKVYV
			YELRQNRFVYNGTLKDSHSYQNARFGSSIASV
1			RDLNQDSYNDVVVGAPLEDNHAGAIYIFHGFR
			GSILKTPKQRITASELATGLQYFGCSIHGQLDLN
		1	EDGLIDLAVGALGNAVILWSRPVVQINASLHFE
			PSKINIFHRDCKRSGRDATCLAAFLCFTPIFLAP
Ì			HFQTTTVGIRYNATMDERRYTPRAHLDEGGDR
			FTNRAVLLSSGQELCERINFHVLDTADYVKPVT
			FSVEYSLEDPDHGPMLDDGWPTTLRVSVPFWN
İ			GCNEDEHCVPDLVLDARSDLPTAMEYCQRVLR
			KPAQDCSAYTLSFDTTVFIIESTRQRVAVEATLE
			NRGENAYSTVLNISQSANLQFASLIQKEDSDGSI
			ECVNEERRLQKQVCNVSYPFFRAKAKVAFRLD
			FEFSKSIFLHHLEIELAAGSDSNERDSTKEDNVA
			PLRFHLKYEVDVLFTRSSSLSHYEVKPNSSLER
			YDGIGPPFSCIFRIQNLGLFPIHGMMMKITIPIAT
			RSGNRLLKLRDFLTDEANTSCNIWGNSTEYRPT
			PVEEDLRRAPQLNHSNSDVVSINCNIRLVPNQEI
			NFHLLGNLWLRSLKALKYKSMKIMVNAALQR
			QFHSPFIFREEDPSRQIVFEISKQEDWQVPIWIIV
			GSTLGGLLLLALLVLALWKLGFFRSARRRREP
			GLDPTPKVLE*
811	261	419	MALNIINPVWFCHCLTCTIHIDFHILFIKIFKHM
			FFRSLWSSWLSHQLDHI*
812	49	282	MAIFPLWKGVNVLVCIFSSFIMLNIYCTLLIWKF
			IYSAFFCYITSLMIFPFSFFCSFFLDLLKVIVYIFF
			LYLYSSR*
813	147	293	MGYLLWLVLSILVCTELGLGRLTFPLDSESPRT
	L	1-73	1.1.0.1.2.5 (1.1.1.1.2.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1

SEQ ID	Predicted	Predicted end	I A wine said assessed association signal montide
NO:	beginning	l .	Amino acid segment containing signal peptide
INO.	nucleotide	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
		location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence		deletion, \=possible nucleotide insertion
			SYKVRPWVVLEAWVW*
814	418	155	MCLSHLVSLFPAATAFLINKVPLPVDKLAPLPL
			DNILPFMDPLKLLLKTLGISVEHLVEGLRKCVN
			ELGPEASEAVKKLLEALSHLV*
815	32	742	MAWIPLFLGVLAYCTGAVASYELTQPPSVSVSP
	\ \frac{1}{2}		GQTASITCSGDRLGDKIACWYQLKPGQSPLVVI
			HQDTKRPSGIPERFSGSNSGNTATLTISGTQAM
			DEADYYCQAWDSSSYVAFGGGTKLTVLGQPK
			AAPSVTLFPPSSEELQANKATLVCLISDFYPGVV
	į		TVAWKADSSPVKAGVETTTPSKQSNNKYAVSS
			•
		,	YLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAP
016	160	1701	TEYLLRVY*
816	160	1701	MPGLGRRAQWLCWWWGLLCSCCGPPPLRPPL
			PAAAAAAGGQLLGDGGSPGRTEQPPPSPQSSS
			GFLYRRLKTQEKREMQKEILSVLGLPHRPRPLH
			GLQQPQPPALRQQEEQQQQQQLPRGEPPPGRL
<u> </u>			KSAPLFMLDLYNALSADNDEDGASEGERQQS
			WPHEAASSSQRRQPPPGAAHPLNRKSLLAPGS
			GSGGASPLTSAQDSAFLNDADMVMSFVNLVEY
			DKEFSPRQRHHKEFKFNLSQIPEGEVVTAAEFRI
			YKDCVMGSFKNQTFLISIYQVLQEHQHRDSDLF
			LLDTRVVWASKEGWLEFDITATSNLWVVTPQH
			NMGLQLSVVTRDGVHVHPRAAGLVGRDGPYD
٠			KQPFMVAFFKVSEVHVRTTRSASSRRRQQSRN
			RSTQSQDVARVSSASDYNSSELKTACRKHELY
			VSFQDLGWQDWIIAPKGYAANYCDGECSFPLN
•	•		AHMNATNHAIVQTLVHLMNPEYVPKPCCAPT
			KLNAISVLYFDDNSNVILKKYRNMVVRACGCH
			*
817	7	942	MGCRLLCCAVLCLLGAVPMETGVTQTPRHLV
"	'	776	MGMTNKKSLKCEQHLGHNAMYWYKQSAKKP
			LELMFVYNFKEQTENNSVPSRFSPECPNSSHLF
	1		LHLHTLQPEDSALYLCASSQVGGYNEQFFGPG
			TRLTVLEDLKNVFPPEVAVFEPSEAEISHTQKA
			TLVCLATGFYPDHVELSWWVNGKEVHSGVST
			DPQPLKEQPALNDSRYCLSSRLRVSATFWQNP
	1		RNHFRCQVQFYGLSENDEWTQDRAKPVTQIVS
			AEAWGRADCGFTSESYQQGVLSATILYEILLGK
			ATLYAVLVSALVLMAMVKRKDSRG*
818	1355	1672	MALLCICLCLIFFLIVKARRKQAAGRPEKMDDE
			DPIMGTITSGSRKKPWPDSPGDQASPPGDAPPL
			EEQKELHYASLSFSEMKSREPKDQEAPSTTEYS
			EIKTSK*

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
• 1	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
1 1	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
1	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid		X=Unknown, *=Stop codon, /=possible nucleotide
1		sequence	deletion, \=possible nucleotide insertion
	sequence	2605	MVVGIVAAAALCILILLYAMYKYRNRDEGSYQ
819	3461	3685	
			VDETRNYISNSAQSNGTLMKEKQQSSKSGHKK
1000	2461	2606	QKNKDREYYV*
820	3461	3685	MVVGIVAAAALCILILLYAMYKYRNRDEGSYQ
			VDETRNYISNSAQSNGTLMKEKQQSSKSGHKK
			QKNKDREYYV*
821	129	272	MGSLMPLRPLALHTALGAALNFSLPCEWSTLPS
			ASEAGRLWGPPSFQ*
822	98	1474	MAWASRLGLLLALLLPVVGASTPGTVVRLNK
			AALSYVSEIGKAPLQRALQVTVPHFLDWSGEA
			LQPTRIRILNVHVPRLHLKFIAGFGVRLLAAANF
]			TFKVFRAPEPLELTLPVELLADTRVTQSSIRTPV
i i			VSISACSLFSGHANEFDGSNSTSHALLVLVQKHI
1			KAVLSNKLCLSISNLVQGVNVHLGTLIGLNPVG
ŀ			PESQIRYSMVSVPTVTSDYISLEVNAVLFLLGKP
			IILPTDATPFVLPRHVGTEGSMATVGLSQQLFDS
1			ALLLLQKAGALNLDITGQLRSDDNLLNTSALG
			RLIPEVARQFPEPMPVVLKVRLGATPVAMLHT
			NNATURLQPFVEVLATASNSAFQSLFSLDVVVN
			LRLQLSVSKVKLQGTTSVLGDVQLTVASSNVG
1			FIDTDQVRTLMGTVFEKPLLDHLNALLAMGIA
			LPGVVNLHYVAPEIFVYEGYVVISSGLFYQS*
823	177	377	MKLVLLRKTSLSVFTTLFSVSSSQYPVLSTSICN
			TPVFSTLFLEACSVNPLPSTVFLVLLYSVACL*
824	1629	1123	MIFVLGQAEGILIMLAMTALTVRRSEPSLSTCQ
			QGEDPLDWTVSLLLMAGLCTFFSCILAVFFHTP
1			YRRLQAESGEPPSTRNAVGSQTQGRVWTEGEA
]			RKGLGSWGPARRIPELHGEGGASLRGPQEGHG
1			SPHPACHRATPRAQGPAATDAPFPPGQTRRQGP
			SVQVY*
825	381	572	MLLAKRYAKYFIYFIFFNPVLIPILQRRILRLGEI
"-"		- / -	HIAGQCRAGSLQSLPLPANLHSILDILA*
826	758	618	MLLCLHLIIICLVFCIISAIPWVLNQCLIFRLYFLC
020	.50	V10	QKKLAMSLEN*
827	184	360	MLIGSGYLCFCALQWTELGNVCVCAHICRCTH
021	107	300	MCIOSOTLEFCALQWIELGNVCVCAHICRETH MQVSGITSPVHVHIHRVLSCLIHFTS*
828	140	355	
020	170	دود	MHLLVSHAFLPFPLHGYSGRQRGAKQWRCHP
		İ	ARASRERPSEDNLSPAVKEESGFVVSEHLAALH
920	21	056	RKLRGCH*
829	21	956	MLLLLLLGLAGSGLGAVVSQHPSWVICKSGT
			SVKIECRSLDFQATTMFWYRQFPKQSLMLMAT
1		Ī	I CALCIEV ATVENTUEV DVELDIUA CLTI CTLTUT
; 1			SNEGSKATYEQGVEKDKFLINHASLTLSTLTVT SAHPEDSSFYICSAGADSGTQETQYFGPGTRLT

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
110.	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence	Sequence	deletion, \=possible nucleotide insertion
	Soquence		VLEDLKNVFPPEVAVFEPSEAEISHTQKATLVC
			LATGFYPDHVELSWWVNGKEVHSGVSTDPOP
			LKEQPALNDSRYCLSSRLRVSATFWQNPRNHF
			RCQVQFYGLSENDEWTQDRAKPVTQIVSAEA
			WGRADCGFTSESYQQGVLSATILYEILLGKATL
			YAVLVSALVLMAMVKRKDSRG*
830	134	292	MSVGLHLGFLAWFLPFLIPTSPLPLLFQLGALPN
		-/-	ESLALYAWLRDCFWENIT*
831	58	258	MSSPCFQCFHLCCTIKVWPLCHHLQKAFPDFSI
051		250	HVFSESDLSSFCEVQLLKICLQKYFLGSLMHCS*
832	68	259	MIKLCHQLYNVYVCFFHLIVLGDIAIDYIIVPNIS
032	00	237	YLSISIPFVVTNIRGRDIFHPCNVALVM*
833	290	430	MFYENKRREYLQDMLLSYRLLVAILVLLKKLT
033	270	1 450	ELNTITLICKSIIF*
834	112	267	MNIVFVILLFKDMQVLEVFVLLNVLTTLTIIAA
77	112	207	GILCTSFCCKPFIYINPL*
835	58	240	MIRFALPWFSQIWLSKQTWTRLTHLAFLLQEC
033	38	240	NSMFYPKVSRTTVFGCLFNPLSSRVCFE*
836	30	296	MTNFFHLLLPLLPSLFSPSSKTHSFNIHKIIIILFF
030	30	290	NSIFLYPRDYLKIRNWLQSNTLEREIEWITSIRCL
			CNSGTTFIFPLTTKST*
837	1089	952	MLYLLLFPGVSYLRSLFLGRPIGPGITSDFTLILF
057	1007	952	SNLLDSWPLS*
838	500	670	MPCSVPETLFSLLWLAPSHHSGFSSNEASLRTD
050	300	070	LLFATAILYSLWHPPYYFLYNTS*
839	84	251	MLFTSFVYGLIFILFDFYFLSFVERDVKIFNCNG
037	0 1	231	EIVLFPFNSVHFCLICLYIHI*
840	99	245	MILNLSSLTLVFAWNYPLHLMISLNVSCSCYSD
040		243	DISGIYRSVLRQKLG*
841	82	297	
041	62	297	MCLILVIWKIHYAELIMLNKRVVNKCRSCLIQK
			CLSTCHSTVIVLYQCREEEAVMLIKLNFKMKIQ RTICI*
842	36	275	1
072	30	2/3	MNLKRLLLFLAKMFSAIFSLPTHPSHFPISIYDNI
	1		GHWPQSPKVRRKEGNEYLLNPNMCQTLDLTLL
843	165	427	GIGDYLTSITSP*
043	201	437	MAPLPSLTLRPWCVLMLLDLWAAFGTITPSLK
			HFHHLPSGTQHSLVFVLSLTLHSQLSLLMGTSA
944	222	463	VCLSACFSSLSTFPGWLLIICTLMI*
844	322	462	MFLLDLCLGSLSVFIDTHPCMHGGFKCSQDWC
0.45	100	250	SPAKLLLSAFTKTR*
845	182	358	MLSLVKLLLLCIIHDHSINFCIAIQVGLLPSAYR
046	-00	005	VPGIVLSLENTALIRQTPCSNRAN*
846	98	805	MRPLAGGLLKVVFVVFASLCAWYSGYLLAELI

SEQ ID NO:	Predicted beginning nucleotide location corresponding to first amino acid residue of amino acid sequence	Predicted end nucleotide location corresponding to first amino acid residue of amino acid sequence	Amino acid segment containing signal peptide (A=Alanine C=Cysteine, D=Aspartic Acid, E=Glutamic Acid, F=Phenylalanine, G=Glycine, H=Histidine, I=Isoleucine, K=Lysine, L=Leucine, M=Methionine, N=Asparagine, P=Proline, Q=Glutamine, R=Arginine, S=Serine, T=Threonine, V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide deletion, \=possible nucleotide insertion  PDAPLSSAAYSIRSIGERPVLKAPVPKRQKCDH WTPCPSDTYAYRLLSGGGRSKYAKICFEDNLL MGEQLGNVARGINIAIVNYVTGNVTATRCFDM YEGDNSGPMTKFIQSAAPKSLLFMVTYDDGST RLNNDAKNAIEALGSKEIRNMKFRSSWVFIAA KGLELPSEIQREKINHSDAKNNRYSGWPAEIQIE GCIPKERS*
847	1608	1805	MLPFCHLWVPVTLVAAGAAQPAASMVMFPHL PALHHHCPHSHRTSQYMPASDGPQAYPDYAD QST*
848	386	592	MNPCFCGFLVLLSCCLSLLDSQLHNLIALQITCF KDVEIPNFFCDPSQLPHHACCDTFTNNIVMYFP AA
849	1074	2294	MLLLLLLPLLWGTKGMEGDRQYGDGYLLQV QELVTVQEGLCVHVPCSFSYPQDGWTDSDPVH GYWFRAGDRPYQDAPVATNNPDREVQAETQG RFQLLGDIWSNDCSLSIRDARKRDKGSYFFRLE RGSMKWSYKSQLNYKTKQLSVFVTDPPWNLT MTVFQGDATASTALGNGSSLSVLEGQSLRLVC AVNSNPPARLSWTRGSLTLCPSRSSNPGLLELP RVHVRDEGEFTCRAQNAQGSQHISLSLSLQNE GTGTSRPVSQVTLAAVGGAGATALAFLSFCIIFI IVRSCRKKSARPAAGVGDTGMEDAKAIRGSAS QGPLTESWKDGNPLKKPPPAVAPSSGEEGELH YATLSFHKVKPQDPQGQEATDSEYSEIKIHKRE TAETQACLRNHNPSSKEVRG*
850	100	318	MYYTLCNFVFFTLHMILFPKSLNILLSNQIRSAI VHLKQRTSCIKNQPEPYQRADAMNTNHSLVAV PYVNLI*
851	328	549	MFWMVKILTPKASTFQVTTSVSVPLTSATGAA CSGSCFHSTGCAGRPQTHAGAPCASEQNSRNE VMQTSTNEM*
852	162	440	MHCRQLKEVLQLPLTCSSCCVCTMTVAFPSVQ QVWMETVLTLGGLDAAQDEIQAVRLILLPESSP QGPHGNLAPCSAKPFFLPQVMPLGTAP*
853	39	839	MVCLRLPGGSCMAVLTVTLMVLSSPLALAGDT RPRFLEYSTSECHFFNGTERVRFLDRYFYNQEE YVRFDSDVGEFRAVTELGRPDEEYWNSQKDFL EDRRAAVDTYCRHNYGVVESFTVQRRVHPKV TVYPSKTQPLQHHNLLVCSVSGFYPGSIEVRWF RNGQEEKTGVVSTGLIHNGDWTFQTLVMLETV PRSGEVYTCQVEHPSVTSPLTVEWRARSESAQS KMLSGVGGFVLGLLFLGAGLFIYFRNQKGHSG

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
INO.	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence		deletion, \=possible nucleotide insertion
			LQPRGFLS*
854	54	1034	MMSPSQASLLFLNVCIFICGEVVQGNCVHHSTD
			SSVVNIVEDGSNAKDESKSNDTVCKEDCEESC
		<u>}</u>	DVKTKITREEKHFMCRNLQNSIVSYTRSTKKLL
			RNMMDEQQASLDYLSNQVNELMNRVLLLTTE
			VFRKQLDPFPHRPVQSHGLDCTDIKDTIGSVTK
			TPSGLYIIHPEGSSYPFEVMCDMDYRGGGWTVI
			QKRIDGIIDFQRLWCDYLDGFGDLLGDAFRGL
			KKEDNQNAMPFSTSDVDNDGCRPACLVNGQS
			VKSCSHLHNKTGWWFNECGLANLNGIHHFSG
			KLLATGIQWGTWTKNNSPVKIKSVSMKIRRMY
			NPYFK*
855	124	336	MRTWSKVIPSLWLKFSRGFIILRFHFLMIIWPDIP
833	124	330	SSMYICMSFITAFKNLFMFGINRIKKISVVSRNT
			L*
056	1.50	1000	
856	159	1028	MGLCVPFAVTTSFLSLGLEWDLNVRLHGQHLV
			QQLVLRTVRGYLETPQPEKALALSFHGWSGTG
			KNFVARMLVENLYRDGLMSDCVRMFIATFHFP
		1	HPKYVDLYKEQLMSQIRETQQLCHQTLFIFDEA
			EKLHPGLLEVLGPHLERRAPEGHRAESPWTIFL
			FLSNLRGDINEVVLKLLKAGWSREEITMEHLE
	•	,	PHLQAEIVETIDNGFGHSRLVKENLIDYFIPFLPL
			EYRHVRLCARDAFLSQELLYKEETLDEIAQMM
			VYVPKEEQLFSSQGCKSISQRINYFLS*
857	182	334	MKSSNIFSLFLFLVTFIFLTSIASILFSSWCPFSLIK
			CNQDLYYSGNGAS*
858	35	172	MLCSLFHILIVTLLLAISFGMSSRNTLNMVNSKI
			KEHSLHRKLEI*
859	6	215	MFWTLVQGMSLLCLTDVFQALPSICIANSEIYY
037	"	213	TVLTLMQFNCLWMVLSGKKVIFSSELMVRKGR
			RSWK*
860	204	350	I
000	204	330	MYLKPLIYFSILIFLSQRSKLSLPYNVHNCMNIG
061	0.0	4.6	EDRRPQKVQLLQLY*
861	263	412	MLPLALIVDLIYPWVQVRGPEDPNHGTTERKR
			EEVTCLGAARLSLEAAR*
862	169	879	MTAEFLSLLCLGLCLGYEDEKKNEKPPKPSLHA
			WPSSVVEAESNVTLKCQAHSQNVTFVLRKVND
1			SGYKQEQSSAENEAEFPFTDLKPKDAGRYFCA
1		1	YKTTASHEWSESSEHLQLVVTDKHDELEAPSM
			KTDTRTIFVAIFSCISILLLFLSVFIIYRCSQHSSSS
1			EESTKRTSHSKLPEQEAAEADLSNMERVSLSTA
1			DPQGVTYAELSTSALSEAASDTTQEPPGSHEYA
		1	ALKV*
L	1	L	1 ADAC V

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence	sequence	deletion, \=possible nucleotide insertion
863	114	1031	MPLLTLYLLLFWLSGYSIATQITGPTTVNGLER
803	114	1031	GSLTVQCVYRSGWETYLKWWCRGAIWRDCKI
			LVKTSGSEQEVKRDRVSIKDNQKNRTFTVTME
		İ	DLMKTDADTYWCGIEKTGNDLGVTVQVTIDP
			1
			ASTPAPTTPTSTTFTAPVTQEETSSSPTLTGHHL
			DNRHKLLKLSVLLPLIFTILLLLLVAASLLAWR
			MMKYQQKAAGMSPEQVLQPLEGDLCYADLTL
		ļ	QLAGTSPQKATTKLSSAQVDQVEVEYVTMASL
			PKEDISYASLTLGAEDQEPTYCNMGHLSSHLPG
			RGPEEPTEYSTISRP*
864	64	435	MRISCPWCLWNLSLEVGGTVATTAQQHIAEVC
			RSSQAGRGFLHCLHPALGTSGCHPVPCSSSLVG
			FGWRGYSGEASWGRASSRPAAPTPPMPANVQ
			AGWEQSVRLLCHSWLRLAALHVTHEES*
865	391	528	MSQQSWFTVYLFYLLRSNIWLEMGIPKYVKEV
			ELRSLDFTSNYFS*
866	46	612	MDWTWRFLFVVAAATGVQSQVQLVQSGAEV
			KKPGSSVKVSCKASGGTFSTYAISWVRQAPGQ
			GLEWMGGIIPIFGTANYAQKFQGRVTITADEST
			STAYMELSSLRSEDTAVYYCARVWGGSGSYYS
			IVSTIGATTTVWMSGAREPWSPSPQPPPRAHRS
			SPWHPPPRAPLGAQRPWAAWSRTTSPNR*
867	46	612	MDWTWRFLFVVAAATGVQSQVQLVQSGAEV
1			KKPGSSVKVSCKASGGTFSTYAISWVRQAPGQ
			GLEWMGGIIPIFGTANYAQKFQGRVTITADEST
			STAYMELSSLRSEDTAVYYCARVWGGSGSYYS
			IVSTIGATTTVWMSGAREPWSPSPQPPPRAHRS
			SPWHPPPRAPLGAQRPWAAWSRTTSPNR*
868	133	960	MACPGFLWALVISTCLEFSMAQTVTQSQPEMS
			VQEAETVTLSCTYDTSESDYYLFWYKQPPSRQ
1			MILVIRQEAYKQQNATENRFSVNFQKAAKSFSL
			KISDSQLGDAAMYFCAYRSGRDDKIIFGKGTRL
			HILPNIQNPDPAVYQLRDSKSSDKSVCLFTDFDS
			QTNVSQSKDSDVYITDKTVLDMRSMDFKSNSA
			VAWSNKSDFACANAFNNSIIPEDTFFPSPESSCD
			VKLVEKSFETDTNLNFQNLSVIGFRILLLKVAG
			FNLLMTLRLWSS*
869	164	310	MVLRLPWWGVLAYGNDVGFGFYSFLCYQINP
		·	PTCPILWLWEVLTVGKS*
870	959	1252	MEFLGPCGLRLVGARPLLPYWLLVFLAALNAL
			LQWLLRPLVLYAPLLNPYTLAVANTTFTVSTD
			KAQRHFGYEPPFSWEDSRTRTILWVQAATGSA
			Q*
L		<u> </u>	1×

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
110.	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location		
	1 -	corresponding to first amino	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	to first amino	acid residue of	M=Methionine, N=Asparagine, P=Proline,
			Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence		deletion, \=possible nucleotide insertion
871	52	828	MPRPRRVSQLLDLCLWCFMKNISRYLTDIKPLP
			PNIKDRLIKIMSMQGQITDSNISEILHPEVQTLDL
			RSCDISDAALLHLSNCRKLKKLNLNASKGNRV
	1		SVTSEGIKAVASSCSYLHEASLKRCCNLTDEGV
			VALALNCQLLKIIDLGGCLSITDVSLHALGKNC
ł	Ī		PFLQCVDFSATQVSDSGVIALVSGPCAKKLEEI
· .			HMGHCVNLTDGAVEAVLTYCPQIRILLFHGCP
			LITDHSREVLEQLVGPNKLKQVTWTVY*
872	313	1704	MLLLLLPLLWGRERAEGQTSKLLTMQSSVTVQ
			EGLCVHVPCSFSYPSHGWIYPGPVVHGYWFRE
			GANTDQDAPVATNNPARAVWEETRDRFHLLG
	1		DPHTENCTLSIRDARRSDAGRYFFRMEKGSIKW
			NYKHHRLSVNVTALTHRPNILIPGTLESGCPQN
			LTCSVPWACEQGTPPMISWIGTSVSPLDPSTTRS
			SVLTLIPQPQDHGTSLTCQVTFPGASVTTNKTV
	1		HLNVSYPPQNLTMTVFQGDGTVSTVLGNGSSL
			SLPEGQSLRLVCAVDAVDSNPPARLSLSWRGL
			TLCPSQPSNPGVLELPWVHLRDEDEFTCRAQNP
			LGSQQVYLNVSLQSKATSGVTQGAVGGAGAT
			ALVFLSFCVIFVVVRSCRKKSARPAAGVGDTGI
		•	EDANAVRGSASQGPLTEPWAEDSPPDQPPPAS
			ARSSVGEGELQYASLSFQMVKPWDSRGQEATD
			TEYSEIKIHR*
873	590	766	MLFGLALQLILDLKLTTVNQRESDVARVATAE
			EYSKKGLLGQETLHAGSQTRMQILIS*
874	206	418	MLKLLCAAEVTNVLFNCVFDYGCPKTFCHPWT
-		,	IFVLFWSSLEGGFIISYKTLTGALECRFLITLEIVT
			SE*
875	241	957	MRSSLTMVGTLWAFLSLVTAVTSSTSYFLPYW
		,	LFGSQMGKPVSFSTFRRCNYPVRGEGHSLIMVE
			ECGRYASFNAIPSLAWQMCTVVTGAGCALLLL
			VALAAVLGCCMEELISRMMGRCMGAAQFVGG
			LLISSGCALYPLGWNSPEIMQTCGNVSNQFQLG
			TCRLGWAYYCAGGGAAAAMLICTWLSCFAGR
			NPKPVILGGKHHEENHFLCYGAWPLPSTLELRK
876	241	957	EDRGGRATGKQVTP
370	~~1	731	MRSSLTMVGTLWAFLSLVTAVTSSTSYFLPYW
			LFGSQMGKPVSFSTFRRCNYPVRGEGHSLIMVE
			ECGRYASFNAIPSLAWQMCTVVTGAGCALLLL
			VALAAVLGCCMEELISRMMGRCMGAAQFVGG
			LLISSGCALYPLGWNSPEIMQTCGNVSNQFQLG
			TCRLGWAYYCAGGGAAAAMLICTWLSCFAGR
			NPKPVILGGKHHEENHFLCYGAWPLPSTLELRK

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
1 1	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
1	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
, ,	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
3 1	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
1 1	sequence	sequence	deletion, \=possible nucleotide insertion
1	sequence		EDRGGRATGKQVTP
877	136	1710	MSLLSLPWLGLRPVAMSPWLLLLLVVGSWLLA
0,7	150	1710	RILAWTYAFYNNCRRLQCFPQPPKRNWFWGH
]			LGLITPTEEGLKDSTQMSATYSQGFTVWLGPIIP
1 1			FIVLCHPDTIRSITNASAAIAPKDNLFIRFLKPWL
		,	GEGILLSGGDKWSRHRRMLTPAFHFNILKSYITI
1 1			FNKSANIMLDKWQHLASEGSSCLDMFEHISLM
			TLDSLQKCIFSFDSHCQERPSEYIATILELSALVE
			KRSQHILQHMDFLYYLSHDGRRFHRACRLVHD
1 1			FTDAVIRERRRTLPTQGIDDFFKDKAKSKTLDFI
			DVLLLSKDEDGKALSDEDIRAEADTFMFGGHD
			TTASGLSWVLYNLARHPEYQERCRQEVQELLK
			DRDPKEIEWDDLAQLPFLTMCVKESLRLHPPAP
1			FISRCCTQDIVLPDGRVIPKGITCLIDIIGVHHNP
1			TVWPDPEVYDPFRFDPENSKGRSPLAFIPFSAGP
1		1	RNCIGQAFAMAEMKVVLALMLLHFRFLPDHTE
[ [			PRRKLELIMRAEGGLWLRVEPLNVSLQ*
878	136	1710	MSLLSLPWLGLRPVAMSPWLLLLLVVGSWLLA
1			RILAWTYAFYNNCRRLQCFPQPPKRNWFWGH
			LGLITPTEEGLKDSTQMSATYSQGFTVWLGPIIP
			FIVLCHPDTIRSITNASAAIAPKDNLFIRFLKPWL
1			GEGILLSGGDKWSRHRRMLTPAFHFNILKSYITI
1			FNKSANIMLDKWQHLASEGSSCLDMFEHISLM
] ]			TLDSLQKCIFSFDSHCQERPSEYIATILELSALVE
			KRSQHILQHMDFLYYLSHDGRRFHRACRLVHD
			FTDAVIRERRRTLPTQGIDDFFKDKAKSKTLDFI
1			DVLLLSKDEDGKALSDEDIRAEADTFMFGGHD
			TTASGLSWVLYNLARHPEYQERCRQEVQELLK
1			DRDPKEIEWDDLAQLPFLTMCVKESLRLHPPAP
			FISRCCTQDIVLPDGRVIPKGITCLIDIIGVHHNP
			TVWPDPEVYDPFRFDPENSKGRSPLAFIPFSAGP
			RNCIGQAFAMAEMKVVLALMLLHFRFLPDHTE
			PRRKLELIMRAEGGLWLRVEPLNVSLQ*
879	136	1710	MSLLSLPWLGLRPVAMSPWLLLLLVVGSWLLA
			RILAWTYAFYNNCRRLQCFPQPPKRNWFWGH
			LGLITPTEEGLKDSTQMSATYSQGFTVWLGPIIP
			FIVLCHPDTIRSITNASAAIAPKDNLFIRFLKPWL
			GEGILLSGGDKWSRHRRMLTPAFHFNILKSYITI
			FNKSANIMLDKWQHLASEGSSCLDMFEHISLM
			TLDSLQKCIFSFDSHCQERPSEYIATILELSALVE
			KRSQHILQHMDFLYYLSHDGRRFHRACRLVHD
			FTDAVIRERRRTLPTQGIDDFFKDKAKSKTLDFI
1 !			DVLLLSKDEDGKALSDEDIRAEADTFMFGGHD

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110.	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
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	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence	sequence	deletion, \=possible nucleotide insertion
	sequence		TTASGLSWVLYNLARHPEYQERCRQEVQELLK
			DRDPKEIEWDDLAQLPFLTMCVKESLRLHPPAP
			FISRCCTQDIVLPDGRVIPKGITCLIDIIGVHHNP
			TVWPDPEVYDPFRFDPENSKGRSPLAFIPFSAGP
:			RNCIGQAFAMAEMKVVLALMLLHFRFLPDHTE
	006	255	PRRKLELIMRAEGGLWLRVEPLNVSLQ*
880	856	257	MRLSLPLLLLLGAWAIPGGLGVMAPLTATAP
			EVDDEEMYSAHMPAHLRCDACRAVAYQECGP
			KTLAKAETKLHTSNSGGRRDVSELVYTDVLDR
			SCSRNWQDYGVREVDQVKRLTGPGLSEGPEPS
			ISVMVTGGPWHTRLSRTCLHYLGEFGEDQIYE
			AHQQGRGALEALLCGGPPGGLLREGVSHKRRA
			LVLDSTLL*
881	782	1222	MTLRPSLLPLHLLLLLLSAAVCRAEAGLETES
			PVRTLQVETLVEPPEPCAEPAAFGDTLHIHYTG
			SLVDGRIIDTSLTRDPLVIELGQKQVIPGLEQSLL
			DMCVGEKRRAIIPSHLAYGKRGFPPSVPGTKDN
			LMRPPGMTSSSQ*
882	940	2040	MALRFLLGFLLAGVDLGVYLMRLELCDPTQRL
			RVALAGELVGVGGHFLFLGLALVSKDWRFLQ
			RMITAPCILFLFYGWPGLFLESARWLIVKRQIEE
			AQSVLRILAERNRPHGQMLGEEAQEALQDLEN
			TCPLPATSSFSFASLLNYRNIWKNLLILGFTNFIA
		-	HAIRHCYQPVGGGGSPSDFYLCSLLASGTAALA
	1		CVFLGVTVDRFGRRGILLLSMTLTGIASLVLLG
			LWDYLNEAAITTFSVLGLFSSQAAAILSTLLAA
			EVIPTTVRGRGLGLIMALGALGGLSGPAQRLH
			MGHGAFLQHVVLAACALLCILSIMLLPETKRK
			LLPEVLRDGELCRRPSLLRQPPPTRCDHVPLLA
			TPNPAL*
883	133	306	MVKRKSWTKWCGWLTVVRFLARGFEMHLKS
			CSRLLFSELAAFAFFEFSLKTVTLRAF*
884	196	357	MCLMKQIIYLLYVGLCSILTAFLFTPHHVLERY
001	1.50	1 22 1	RYYCPDFREIKKLGQGYTTN*
885	252	560	MKEALLKCSRLARGLLLCLDCANDHRSPVERN
003	232	300	AQTTLILHSSLYSLSLGNQLQGGEMATTGGST
			QQAKTYGGLFQIGAMEPALFLLFIFLLASFWVH
			RAIE*
886	46	190	
000	40	189	MLETFLFKLFLFFTLLVNLFITNDQLSVGSIFLSF
007	(0)	200	QLPAFFLDMAEF*
887	68	208	MTFLLHVLVTALSSHSTGRRGTNCFMLLSSGN
000		200	HPIPCGSLTPYPHL*
888	214	399	MVYLPVSLNGLRLACFSYVLAPIKVKPGGGSET

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
NO.	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
		to first amino	M=Methionine, N=Asparagine, P=Proline,
ł	corresponding	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	to first amino		V=Valine, W=Tryptophan, Y=Tyrosine,
	acid residue	amino acid	X=Unknown, *=Stop codon, /=possible nucleotide
	of amino acid	sequence	deletion, \=possible nucleotide insertion
	sequence		
			RDGFRIPESTPSLKAGYCDHKHFLPTIHL
889	50	214	MTLLNLYYLNSFLLYSKRFEGISFCVQKVSIILCI
			HYLRSTTIWNKLFFRDVSA*
890	158	700	MHFPVNCFFKSLHIFLLLQVFLATFLRKKLSKV
			AFSCLVEFFYYCYYFLDFASSVSFLFCFVLLLRQ
1			SLTLSPRLECSDTILAHCNLRLPGSRYSSASTSR
			VAGITGVHHHTYVNFVWTVQKAVHCVGQAS
			WELLTSRDPPTLASHRAGITGMSHRTWAKVFL
			KRVIFLNREYDLTMFCFL
891	133	333	MLVPTFLSLVCDFSLFVLLLLGCLSFLLPPHLPC
			TSFPLHLWRLLSPFISFLDLLLLLSYKMNCII*
892	71	295	MLPLFKHSPVRIFLFCLNTQHLSVRNNFVFNCV
			SPGILPISLCLAFNHDRSTFFFSIILLLKALIILSSL
ļ			LQTK*
893	95	331	MKPILLVLSSITRALLLQISSVSWQSCMWRAMP
0,5			DCLQTDYPISLGFHQRTRLLDALCPVTQCHHSA
1			WPCVCQGAQTPI*
894	182	418	MCCELLAVVIATLIIKIGLVVLLYFIKLLIHIEFIK
07.	1.02		RHSILKCESIFNLNVGIRMYPGQVNFCETLQML
			DGFGRIFQTK
895	104	2683	MACRWSTKESPRWRSALLLLFLAGVYGNGAL
10,3	10,	2003	AEHSENVHISGVSTACGETPEQIRAPSGIITSPG
	İ		WPSEYPAKINCSWFIRANPGEIITISFQDFDIQGS
		,	RRCNLDWLTIETYKNIESYRACGSTIPPPYISSQ
1			DHIWIRFHSDDNISRKGFRLAYFSGKSEEPNCA
			CDQFRCGNGKCIPEAWKCNNMDECGDRSDEEI
1			CAKEANPPTAAAFQPCAYNQFQCLSRFTKVYT
			CLPESLKCDGNIDCLDLGDEIDCDVPTCGQWL
			KYFYGTFNSPNYPDFYPPGSNCTWLIDTGDHR
			KVILRFTDFKLDGTGYGDYVKIYDGLEENPHK
			LLRVLTAFDSHAPLTVVSSSGQIRVHFCADKVN
			AARGFNATYQVDGFCLPWEIPCGGNWGCYTE
		1	OQRCDGYWHCPNGRDETNCTMCQKEEFPCSR
			NGVCYPRSDRCNYQNHCPNGSDEKNCFFCQPG
1			NGVC TPRSDRCM TQMTCT NGSDERIVETT EQTO NFHCKNNRCVFESWVCDSQDDCGDGSDEENC
			PVIVPTRVITAAVIGSLICGLLLVIALGCTCKLYS
			LRMFERRSFETQLSRVEAELLRREAPPSYGQLI
1			AQGLIPPVEDFPVCSPNQASVLENLRLAVRSQL
			GFTSVRLPMAGRSSNIWNRIFNFARSRHSGSLA
			LVSADGDEVVPSQSTSREPERNHTHRSLFSVES
			DDTDTENERRDMAGASGGVAAPLPQKVPPTTA
		1	VEATVGACASSSTQSTRGGHADNGRDVTSVEP
L			PSVSPARHQLTSALSRMTQGLRWVRFTLGRSSS

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
INO.	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
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	1	to first amino	M=Methionine, N=Asparagine, P=Proline,
	corresponding to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue	amino acid	
			V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence		deletion, \=possible nucleotide insertion
			LSQNQSPLRQLDNGVSGREDDDDVEMLIPISDG
•			SSDFDVNDCSRPLLDLASDQGQGLRQPYNATN
			PGVRPSNRDGPCERCGIVHTAQIPDTCLEVTLK
906	220	201	NETSDDEALLLC* MSNRTRIRTHVNLCCFCRYTTPKMSFSSACVSL
896	230	391	
207	45	1147	CLMLLFCSPPLLLLLSSFV*
897	47	1147	MASMAAVLTWALALLSAFSATQARKGFWDYF
			SQTSGDKGRVEQIHQQKMAREPATLKDSLEQD
			LNNMNKFLEKLRPLSGSEAPRLPQDPVGMRRQ
			LQEELEEVKARLQPYMAEAHELVGWNLEGLR
	-		QQLKPYTMDLMEQVALRVQELQEQLRVVGED
			TKAQLLGGVDEAWALLQGLQSRVVHHTGRFK
			ELFHPYAESLVSGIGRHVQELHRSVAPHAPASP
			ARLSRCVQVLSRKLTLKAKALHARIQQNLDQL
			REELSRAFAGTGTEEGAGPDPQMLSEEVRQRL
			QAFRQDTYLQIAAFTRAIDQETEEVQQQLAPPP
			PGHSAFAPEFQQTDSGKVLSKLQARLDDLWED
			ITHSLHDQGHSHLGDP*
898	493	636	MFIGLGISFLNCPSLFAHFILFCPLPLFGIFISYWF VRLLSINRGWK*
899	92	1195	MEFGLSWLFLVAILKGVQCEVQLVESGGGLVQ
			PGGSLRLSCAASGFTFSSYAMSWVRQAPGKGL
			EWVSGFTGSGGSGGSTYYADSVKGRFTISRDN
			SKNTLFLQMNSLRAEDTAVYYCAKGLLPPRW
			AYRVYEDSGIFFDYWGQGTLVTVSSSDIQMTQ
			SPSTLSASVGDRVTITCRASQSISSWLAWYQQK
		·	PGKAPKLLIYKASSLQSGVPSRFSGSGSGTDFTL
			TISSLQPDDFATYYCQQLSTYVWTFGQGTKVDI
			KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF
			YPREAKVQWKVDNALQSGNSQESVTEQDSKD
		·	STYSLSSTLTLSKADYEKHKVYACEVTHQGLSS
			PVTKSFNRGEC*
900	948	1115	MLCGNTQLLFTVAIILLYVTCLLHWTFLHLEW
	]		RVSEGRHHDPLSTTLMHEKMNDN*
901	722	84	MYRLSSSMLLRALAQAMRTGHLIGQSLHSSAV
			AATYKYVNKKEQESEVDMKSETDNAARILMW
			TELIRGLGMTLRYLFREPATINYPFEKGPLSPRF
			RGEHALRRYPSGEERCIACKLCEAICPAQAITIE
			AEPRADGSRRTTRYDIDMTKCIYCGFCQEACPV
			DAIVEGPNFEFSTETHEELLYNKEKLLNNGDK
			WEAEIAANIQADYLYR*
902	50	259	MIELAFASFLKCASFSLLILFSFSFPLWFFLSCFA
702	] 30	239	CSYSFSCLLSRISILSPFCHLLPRQSHDLCTNDL*
L	L	<u> </u>	CO LOLOCITORIOLESI L'CUTTL' MÁDITECTUAT.

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
110.	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence	Sequence	deletion, \=possible nucleotide insertion
903	194	382	MSVLIWCLIFFPLEYSRPKRGLKVDNVCFSTVA
903	194	362	LSTGSRISNWSNCETCLLAEMFFLDLGFS*
904	44	1000	MAAAAVSGALGRAGWRLLQLRCLPVARCRQA
704	77	1000	LVPRAFHASAVGLRSSDEQKQQPPNSFSQQHSE
			TOGAEKPDPESSHSPPRYTDQGGEEEEDYESEE
			QLQHRILTAALEFVPAHGWTAEAIAEGAQSLG
			LSSAASMFGKDGSELILHFVTQCNTRLTRVLE
			EEOKLVOLGOAEKRKTDQFLRDAVETRLRMLI
			PYIEHWPRALSILMLPHNIPSSLSLLTSMVDDM
			WHYAGDQSTDFNWYTRRAMLAAIYNTTELVM
			MODSSPDFEDTWRFLENRVNDAMNMGHTAK
			QVKSTGEALVQGLMGAAVTLKNLTGLNQRR*
905	127	297	MGHLLCVWGFTYILPCISLRHSPLQPPGWEGFC
303	127	291	RNVSFPLLRASLAPHHRRKDGFI*
906	233	484	MHVLIRTPCSLILCLANSSHASLPGFSASSFLFK
300	233	707	ESCRLLINSSFLLHGLEILSGAIAGQCNSFCLFSI
			SQGSLSFNASCPLP*
907	572	787	MTLLWPHTAACLSVTLYLPASSAKYFKRGEGR
70,	" -	, , ,	EKFITNPTTRKKKLFWRRGKRNHDQAFTGIPDQ
			VSLFPF*
908	259	552	MYLHVLVLSHRILLSPYIPSFKSVPPPVFSILQM
			APMSILDIDHPRSLGGDSSHFFSSVAQALTFCPF
į			ALRPFNNYSLQRPVFQKAPAFHHFLVKKF*
909	99	371	MFLVFCNIITVITMTSLFLILLSCIFILITCCYKCR
			YISFSFTFSVTPSGFFVSILQYLAHILLLITLQFHF
:			RVCYVNIITLIPLAQIFL*
910	102	278	MOLWGFLNLNFPCSSLCFWALGSRGFTLVLAV
			TPINSTGWAAHLPQHVKMRLFSIQLF*
911	142	360	MLMVLKLVICSIFIGKEGHFVISYLPSFSLNIQDT
			LKSVHQPCSALSGYNMPEKPEECSIKERHPYSQ
			RLFLE
912	191	481	MGISCKLLLLTRVCYLITPLDLERFPFPNTEQVT
			FPERRVSVFLLPLSWCLDTRLPREPGCRCRHSSP
1			QDVVGGSHLVTTTLLSLPAREFWTSCIL*
913	256	393	MILFHCEKLYALRSFDFWFMLELLSTWPRALG
			LLCPGLAIEAHEG*
914	29	265	MKTLKIFTYYFLSLSNIFILTIGLTCASGPLDFTP
			VFLLGKGSLKCKYGPVAHLPPEALESGPQIPSG
			CNWKEIPTSS*
915	79	339	MWLFCAWVSTWGQGCPPGRGQMIYASHHLSV
	1.		HTTSPHHWLSAWALQGGAVFPELAHGASSASS
			GQADDSTCSFCSPWRVSAEHKSLT
916	57	1163	MWPALLLSHLLPLWPLLLLPLPPPAQDSSSSPR
L <u>´.`</u>	17.	11103	THE PROPERTY OF THE PROPERTY O

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
110.	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid		X=Unknown, *=Stop codon, /=possible nucleotide
	1	sequence	deletion, \=possible nucleotide insertion
<u> </u>	sequence		TPPAPARPPCARGGPSAPRHVCVWERAPPPSRS
			PRVPRSRRQVLPGTAPPATPSGFEEGPPSSQYP
			WAIVWGPTVSREDGGDPNSANPGFLDYGFAAP
ŀ			HGLATPHPNSDSMRGDGDGLILGEAPATLRPFL
			FGGRGEGVDPQLYVTITISIIIVLVATGIIFKFCW
			DRSQKRRPSGQQGALRQEESQQPLTDLSPAG
			VTVLGAFGDSPTPTPDHEEPRGGPRPGMPHPKG
			APAFQLNRSLSGQRFLHTLPLMCVSRPDVVVV
			CGVLTLSLMNTHPPRFRSPCMLLQRWVGGELG
			APWALIGHGLVPFHTICFSVSPSYSKDAGITLRA
			PPWEMG*
917	427	1461	MDFLVLFLFYLASVLMGLVLICVCSKTHSLKGL
}			ARGGAQIFSCIIPECLQRAMHGLLHYLFHTRNH
			TFIVLHLVLQGMVYTEYTWEVFGYCQELELSL
			HYLLLPYLLLGVNLFFFTLTCGTNPGIITKANEL
			LFLHVYEFDEVMFPKNVRCSTCDLRKPARSKH
			CSVCNWCVHRFDHHCVWVNNCIGAWNIRYFL
			IYVLTLTASAATVAIVSTTFLVHLVVMSDLYQE
			TYIDDLGHLHVMDTVFLIQYLFLTFPRIVFMLG
		}	FVVVLSFLLGGYLLFVLYLAATNQTTNEWYRG
			DWAWCQRCPLVAWPPSAEPQVHRNIHSHGLR
			SNLQEIFLPAFPCHERKKQE*
918	251	538	MELVLVFLCSLLAPMVLASAAEKEKEMDPFHY
			DYQTLRIGGLVFAVVLFSVGILLILSRRCKCSFN
			QKPRAPGDEEAQVENLITANATEPQKAEN*
919	1355	1507	MGRRKFLPPPLLSLLSSSLPLPICHPPAPLTPGLG
			IPPCGVVGREVFSVL*
920	588	292	MRAVLLQHLFILLDRQTTKKNSNLDIGHVFREA
			LIFLADLKSQLPSVTHHQYRHLPSNWLQLLQCG
			QDKHCCLSHARLGLAQDIHSQNGLRDALMLDF
			*
921	588	292	MRAVLLQHLFILLDRQTTKKNSNLDIGHVFREA
	1		LIFLADLKSQLPSVTHHQYRHLPSNWLQLLQCG
		·	QDKHCCLSHARLGLAQDIHSQNGLRDALMLDF
			*
922	288	1346	MRSLGALLLLLSACLAVSAGPVPTPPDNIQVQE
			NFNISRIYGKWYNLAIGSTCPWLKKIMDRMTV
			STLVLGEGATEAEISMTSTRWRKGVCEETSGA
	}		YEKTDTDGKFLYHKSKWNITMESYVVHTNYD
			EYAIFLTKKFSRHHGPTITAKLYGRAPQLRETLL
			QDFRVVAQGVGIPEDSIFTMADRGECVPGEQEP
			EPILIPRVRRAVLPQEEEGSGGGQLVTEVTKKE
			DSCQLGYSAGPCMGMTSRYFYNGTSMACETF
L	L	<u> </u>	200 QUO TOTO CONTOUNT OF THO TOWN MODIF

SEQ ID	Predicted	Predicted end	Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
110.	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue		V=Valine, W=Tryptophan, Y=Tyrosine,
		amino acid	
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence		deletion, \=possible nucleotide insertion
			QYGGCMGNGNNFVTEKECLQTCRTVAACNLPI
			VRGPCRAFIQLWAFDAVKGKCVLFPYGGCQG
			NGNKFYSEKECREYCGVPGDGDEELLRFSN*
923	510	1880	MFLLLPFDSLIVNLLGISLTVLFTLLLVFIIVPAIF
-			GVSFGIRKLYMKSLLKIFAWATLRMERGAKEK
			NHQLYKPYTNGIIAKDPTSLEEEIKEIRRSGSSK
			ALDNTPEFELSDIFYFCRKGMETIMDDEVTKRF
			SAEELESWNLLSRTNYNFQYISLRLTVLWGLG
			VLIRYCFLLPLRIALAFTGISLLVVGTTVVGYLP
			NGRFKEFMSKHVHLMCYRICVRALTAIITYHD
			RENRPRNGGICVANHTSPIDVIILASDGYYAMV
			GQVHGGLMGVIQRAMVKACPHVWFERSEVKD
			RHLVAKRLTEHVQDKSKLPILIFPEGTCINNTSV
			MMFKKGSFEIGATVYPVAIKYDPQFGDAFWNS
			SKYGMVTYLLRMMTSWAIVCSVWYLPPMTRE
			ADEDAVQFANRVKSAIARQGGLVDLLWDGGL
			KREKVKDTFKEEQQKLYSKMIVGNHKDRSRS*
924	56	1459	MLLLLLPLLWGRERVEGQKSNRKDYSLTMQS
			SVTVQEGMCVHVRCSFSYPVDSQTDSDPVHGY
			WFRAGNDISWKAPVATNNPAWAVQEETRDRF
			HLLGDPQTKNCTLSIRDARMSDAGRYFFRMEK
			GNIKWNYKYDQLSVNVTALTHRPNILIPGTLES
			GCFQNLTCSVPWACEQGTPPMISWMGTSVSPL
			HPSTTRSSVLTLIPQPQHHGTSLTCQVTLPGAG
			VTTNRTIQLNVSYPPQNLTVTVFQGEGTASTAL
			GNSSSLSVLEGQSLRLVCAVDSNPPARLSWTW
	İ		RSLTLYPSQPSNPLVLELQVHLGDEGEFTCRAQ
			NSLGSQHVSLNLSLQQEYTGKMRPVSGVLLGA
			VGGAGATALVFLSFCVIFIVVRSCRKKSARPAA
			DVGDIGMKDANTIRGSASQGNLTESWADDNPR
			HHGLAAHSSGEEREIQYAPLSFHKGEPQDLSGQ
			EATNNEYSEIKIPK*
925	56	1459	
123	30	1737	MLLLLLPLLWGRERVEGQKSNRKDYSLTMQS
			SVTVQEGMCVHVRCSFSYPVDSQTDSDPVHGY
			WFRAGNDISWKAPVATNNPAWAVQEETRDRF
			HLLGDPQTKNCTLSIRDARMSDAGRYFFRMEK
			GNIKWNYKYDQLSVNVTALTHRPNILIPGTLES
		+	GCFQNLTCSVPWACEQGTPPMISWMGTSVSPL
			HPSTTRSSVLTLIPQPQHHGTSLTCQVTLPGAG
			VTTNRTIQLNVSYPPQNLTVTVFQGEGTASTAL
	}		GNSSSLSVLEGQSLRLVCAVDSNPPARLSWTW
			RSLTLYPSQPSNPLVLELQVHLGDEGEFTCRAQ
<u></u>		<u></u>	NSLGSQHVSLNLSLQQEYTGKMRPVSGVLLGA

CEO ID	Predicted	Predicted end	I Amino and according a constraint
SEQ ID			Amino acid segment containing signal peptide
NO:	beginning	nucleotide	(A=Alanine C=Cysteine, D=Aspartic Acid,
	nucleotide	location	E=Glutamic Acid, F=Phenylalanine, G=Glycine,
	location	corresponding	H=Histidine, I=Isoleucine, K=Lysine, L=Leucine,
	corresponding	to first amino	M=Methionine, N=Asparagine, P=Proline,
	to first amino	acid residue of	Q=Glutamine, R=Arginine, S=Serine, T=Threonine,
	acid residue	amino acid	V=Valine, W=Tryptophan, Y=Tyrosine,
	of amino acid	sequence	X=Unknown, *=Stop codon, /=possible nucleotide
	sequence		deletion, \=possible nucleotide insertion
			VGGAGATALVFLSFCVIFIVVRSCRKKSARPAA
			DVGDIGMKDANTIRGSASQGNLTESWADDNPR
			HHGLAAHSSGEEREIQYAPLSFHKGEPQDLSGQ
			EATNNEYSEIKIPK*
926	167	403	MRMLLTLGGLPQMCLKFHGTPLTCPQGVPCPH
			DSQRIQGIPKAPTGREFLAGPQRVPFPWLRSPA
			HVRGQPSPGGPTPG
927	161	415	MLCWKTTSGRLKDILAILLTDVLLLLQEKDQK
			YVFASVDSKPPVISLQKLIVREVANEEKAMFMI
			SASLQGPECIAAAREDPSKQ
928	159	365	MQQPEVKTWGGVVTAAMVIALAVYMGTGICG
			FLTFGAAVDPDVLLSYPSEDMAVAVARALIILS
			VLTCI
929	1377	1237	MQMWWLGAQSAGRCWLRARTATSWWTCSW
,_,	.5,,	1237	KRLVRGCCGRKTSSLVW*
930	1524	1673	MRNLSQRVTFRMVFAACSRYSRNMQPCCVLIF
750	1321	1075	LKILLCLFYQSVGQFAN*
931	126	413	MSLCLAFLLHWGHFRTCPLSHVEMHLYPKRCP
,,,,		113	QRNAESRWSPALVHCSRHIVQVSPSSSSIEAEGS
			RGSDFWGDGCLGRVLPPSIHVTSCSAETPA
932	49	615	MVPGAAGWCCLVLWLPACVAAHGFRIHDYLY
754	17	013	FQVLSPGDIRYIFTATPAKDFGGIFHTRYEQIHL
		-	VPAEPPEACGELSNGFFIQDQIALVERGGCSFLS
			KTRVVQEHGGRAVIISDNAVDNDSFYVEMIQD
			STQRTADIPALFLLGRDGYMIRRSLEQHGLPWA
			IISIPVNVTSIPTFELLQPPWTFW*
933	1444	1622	
733	1444	1632	MACCLPCRAFPAYPTGVWPTTWLWCWAVLPI
			PWPASWPWVCCAGPWQGWAASLCWACSVGA
934	442	142	1
934	442	143	MDWNLQFSLLLWATADISDQLFQPPQKFSWDP
			LESALCLYSSGSAKDLKGEMQSFWYPARKSPP
			LHLPALQLFYFGELPCKFLPALVVPGSTLPPSRP
			L*
935	52	309	MKITGGLLLLCTVVYFCSSSEAASLSPKKVDCSI
			YKKYPVVAIPCPITYLPVCGSDYITYGNECHLC
			TESLKSNGRVQFLHDGSC*
936	26	1057	MWAAAGGLWRSRAGLRALFRSRDAALFPGCE
			RGLHCSAVSCKNWLKKFASKTKKKVWYESPS
			LGSHSTYKPSKLEFLMRSTSKKTRKEDHARLR
			ALNGLLYKALTDLLCTPEVSQELYDLNVELSK
			VSLTPDFSACRAYWKTTLSAEQNAHMEAVLQ
			RSAAHMRHLLMSQQTLRNVPPIVFVQDKGNA
			ALAELDQLLAVADFGPRDERDNFVQNDFRDPD
			( ) ( ) ( ) ( ) ( ) ( ) ( ) ( ) ( ) ( )

SEQ ID NO:	Predicted beginning nucleotide location corresponding to first amino acid residue of amino acid sequence	Predicted end nucleotide location corresponding to first amino acid residue of amino acid sequence	Amino acid segment containing signal peptide (A=Alanine C=Cysteine, D=Aspartic Acid, E=Glutamic Acid, F=Phenylalanine, G=Glycine, H=Histidine, I=Isoleucine, K=Lysine, L=Leucine, M=Methionine, N=Asparagine, P=Proline, Q=Glutamine, R=Arginine, S=Serine, T=Threonine, V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide deletion, \=possible nucleotide insertion APQPCGTTEPTTSSSLCGIDHEALNKQIMEYKR RKDKGLGGLVWQGQVAELTTQMQKGRKRAK PRLEQDSSLKSYLSGEEVEDDLDLVGAPEYECY
937	271	98	APDTEELEAERGGGRTEDGHSCGASRE*  MTAQHHSIAVLLLNLEVTCECMEYNKVFYSGS FASTSFLIGYCSSSSGFYFVQPSRP*
938	140	370	MLAHLSFERSLILHLIFSGIAVSIKALTKTWMPP EMGSSPVYKAFSLLQCRLSAQKWGSCHSQNTL HWPVWGPQTTL
939	100	411	MALLHICVGHPLLSFPKAGDFSFSSQDDPSELT AGAKDKEFSCLLVICLQPAPSTRSLFSWQLFLLS FSLVSFTLIYRGEFKKSGEAKDYLTQVQGPIDC GKLL
940	111 .	386	MFRSNPGFFFFCCCKSCILAISLGEIPRNEFTEN MSLRESEDLKPDLSAFKSSALYTDVSSPVFFTY QNSRTLPEKPGRYCSTPVSCFSPG*
941	92	328	MCRLYSCARMPLFSTVLFSNVYINDFLLQKPEN TTSQPLSNQRVVEVAIPHVGKFMIESKEGGYDD EVPFTALCTIAT*
942	143	481	MGIQWTCEWPSSLSPGWKFIACLWFSMWGSRP PLSQAMSHKQWPMLCSSISNPEASGTELFTYHF HMMGYIERFWPTEELAQRCSLHKELPCTVFTE KHCSCTFLMVFGVCT*
943	956	1558	MQGMKTQLIQLSTLLRLLDSGFCSYLESQDSGY LYFCFRWLLIRFKREFSFLDILRLWEVMWTELP CTNFHLLLCCAILESEKQQIMEKHYGFNEILKHI NELSMKIDVEDILCKAEAISLQMVKCKELPQAV CEILGLQGSEVTTPDSDVGEDENVVMTPCPTSA FQSNALPTLSASGARNDSPTQIPVSSDVCRLTPA *
944	23	319	MGASLALGFTEVVLVLGFTVKLGAHLTLLPPL GGHLSPYCAAQAWEGVKQLMCNCSSYPLQCII CCIYATPGCYNLSFGILSSCEGIFVYEWLFEMLL *

## WHAT IS CLAIMED IS:

- 1. An isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of SEQ ID NO:1-236 and 473-708, a mature protein coding portion of SEQ ID NO:1-236 and 473-708, an active domain coding portion of SEQ ID NO:1-236 and 473-708, and complementary sequences thereof.
- 2. An isolated polynucleotide encoding a polypeptide with biological activity, wherein said polynucleotide hybridizes to the polynucleotide of claim 1 under stringent hybridization conditions.
- 3. An isolated polynucleotide encoding a polypeptide with biological activity, wherein said polynucleotide has greater than about 90% sequence identity with the polynucleotide of claim 1.
- 4. The polynucleotide of claim 1 wherein said polynucleotide is DNA.
- 5. An isolated polynucleotide of claim 1 wherein said polynucleotide comprises the complementary sequences.
- 6. A vector comprising the polynucleotide of claim 1.
- 7. An expression vector comprising the polynucleotide of claim 1.
- 8. A host cell genetically engineered to comprise the polynucleotide of claim 1.
- 9. A host cell genetically engineered to comprise the polynucleotide of claim 1 operatively associated with a regulatory sequence that modulates expression of the polynucleotide in the host cell.
- 10. An isolated polypeptide, wherein the polypeptide is selected from the group consisting of:

(a) a polypeptide encoded by any one of the polynucleotides of claim 1; and

- (b) a polypeptide encoded by a polynucleotide hybridizing under stringent conditions with any one of SEQ ID NO:1-236 and 473-708.
- 11. A composition comprising the polypeptide of claim 10 and a carrier.
- 12. An antibody directed against the polypeptide of claim 10.
- 13. A method for detecting the polynucleotide of claim 1 in a sample, comprising:
- a) contacting the sample with a compound that binds to and forms a complex with the polynucleotide of claim 1 for a period sufficient to form the complex; and
- b) detecting the complex, so that if a complex is detected, the polynucleotide of claim 1 is detected.
- 14. A method for detecting the polynucleotide of claim 1 in a sample, comprising:
- a) contacting the sample under stringent hybridization conditions with nucleic acid primers that anneal to the polynucleotide of claim 1 under such conditions;
- b) amplifying a product comprising at least a portion of the polynucleotide of claim 1; and
- c) detecting said product and thereby the polynucleotide of claim 1 in the sample.
- 15. The method of claim 14, wherein the polynucleotide is an RNA molecule and the method further comprises reverse transcribing an annealed RNA molecule into a cDNA polynucleotide.
- 16. A method for detecting the polypeptide of claim 10 in a sample, comprising:

 a) contacting the sample with a compound that binds to and forms a complex with the polypeptide under conditions and for a period sufficient to form the complex; and

- b) detecting formation of the complex, so that if a complex formation is detected, the polypeptide of claim 10 is detected.
- 17. A method for identifying a compound that binds to the polypeptide of claim 10, comprising:
- a) contacting the compound with the polypeptide of claim 10 under conditions sufficient to form a polypeptide/compound complex; and
- b) detecting the complex, so that if the polypeptide/compound complex is detected, a compound that binds to the polypeptide of claim 10 is identified.
- 18. A method for identifying a compound that binds to the polypeptide of claim 10, comprising:
- a) contacting the compound with the polypeptide of claim 10; in a cell, under conditions sufficient to form a polypeptide/compound complex, wherein the complex drives expression of a reporter gene sequence in the cell; and
- b) detecting the complex by detecting reporter gene sequence expression, so that if the polypeptide/compound complex is detected, a compound that binds to the polypeptide of claim 10 is identified.
- 19. A method of producing the polypeptide of claim 10, comprising,
- a) culturing a host cell comprising a polynucleotide sequence selected from the group consisting of a polynucleotide sequence of SEQ ID NO:1-236 and 473-708, a mature protein coding portion of SEQ ID NO:1-236 and 473-708, an active domain coding portion of SEQ ID NO:1-236 and 473-708, complementary sequences thereof and a polynucleotide sequence hybridizing under stringent conditions to SEQ ID NO:1-236 and 473-708, under conditions sufficient to express the polypeptide in said cell; and
  - b) isolating the polypeptide from the cell culture or cells of step (a).

20. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of any one of the polypeptides SEQ ID NO:237-472 and 709-944, the mature protein portion thereof, or the active domain thereof.

- 21. The polypeptide of claim 20 wherein the polypeptide is provided on a polypeptide array.
- 22. A collection of polynucleotides, wherein the collection comprising the sequence information of at least one of SEQ ID NO:1-236 and 473-708.
- 23. The collection of claim 22, wherein the collection is provided on a nucleic acid array.
- 24. The collection of claim 23, wherein the array detects full-matches to any one of the polynucleotides in the collection.
- 25. The collection of claim 23, wherein the array detects mismatches to any one of the polynucleotides in the collection.
- 26. The collection of claim 22, wherein the collection is provided in a computerreadable format.
- 27. A method of treatment comprising administering to a mammalian subject in need thereof a therapeutic amount of a composition comprising a polypeptide of claim 10 or 20 and a pharmaceutically acceptable carrier.
- 28. A method of treatment comprising administering to a mammalian subject in need thereof a therapeutic amount of a composition comprising an antibody that specifically binds to a polypeptide of claim 10 or 20 and a pharmaceutically acceptable carrier.

## SEQUENCE LISTING

<110>	Hyseq, Inc. Tang et al	
<120>	Novel Nucleic Acids and Polypeptides	
<130>	21272-017 (785)	
	not yet assigned 2001-01-25	
	09/491,404 2000-01-25	
	09/617,746 2000-07-17	
	09/631,451 2000-08-03	
	09/633,870 2000-09-15	
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	gtctgggctg ctcccgcgga gggcctgggc ggacgcggg atg ctg  Met Leu  1	115
ggg gtc cgc Gly Val Arg 5	c tgc ctg ctg cgg tcc gtg cgc ttc tgt tcc tcc	163
ttc ccc aag Phe Pro Lys 20	g cac aaa cct tca gcc aaa ctg agc gtg cgg gac gct ctc s His Lys Pro Ser Ala Lys Leu Ser Val Arg Asp Ala Leu 25	211
ggg gct cag Gly Ala Gln 35	g aac gcg agt ggg gag cgc att aag atc cag gga tgg att n Asn Ala Ser Gly Glu Arg Ile Lys Ile Gln Gly Trp Ile 40 45 50	259
cgt tct gtc Arg Ser Val	c cga tcc cag aag gaa gtc ttg ttc ctg cat gta aat gat L Arg Ser Gln Lys Glu Val Leu Phe Leu His Val Asn Asp 55 60 65	307
ggg tca tct Gly Ser Ser	ttg gaa agc ctt cag gtt gtt gca gat tca ggc ctt gac Leu Glu Ser Leu Gln Val Val Ala Asp Ser Gly Leu Asp 70 75 80	355

wc	01/5	5437												r	C1/03	01/02023
						GJ À aaa										403
ata Ile	aaa Lys 100	agt Ser	cca Pro	tcc Ser	aaa Lys	agg Arg 105	caa Gln	aat Asn	gtg Val	gaa Glu	ctg Leu 110	aag Lys	gca Ala	gaa Glu	aaa Lys	451
att Ile 115	aaa Lys	gtt Val	att Ile	gga Gly	aat Asn 120	tgt Cys	gat Asp	gcc Ala	aag Lys	gat Asp 125	ttc Phe	ccc Pro	atc Ile	aaa Lys	tat Tyr 130	499
aaa Lys	gag Glu	agg Arg	cat His	cct Pro 135	ctg Leu	gag Glu	tac Tyr	ctg Leu	cga Arg 140	caa Gln	tat Tyr	cct Pro	cac His	ttt Phe 145	agg Arg	547
						ggt Gly			Leu							595
						ttc Phe										643
						tcc Ser 185		_						_		691
						ggc Gly										739
						tta Leu										787
	_			_		act Thr										835
			Asn			agc Ser										883
		Ala				ttt Phe 265										931
-	Ile		_			aag Lys	_				Met					979
_		-	_	_	Glu	ctc Leu	-			Phe		-			Gln	1027
				Glu		atg Met								Ile		1075
			Ala			atc Ile		Lys					Asn			1123

w	01/5	5437												ì	PCT/US	01/02623
ttt Phe	acc Thr 340	cca Pro	gag Glu	tgg Trp	ggt Gly	gct Ala 345	gac Asp	cta Leu	cgg Arg	act Thr	gaa Glu 350	cat His	gaa Glu	aag Lys	tac Tyr	1171
ctg Leu 355	gtg Val	aag Lys	cac	tgt Cys	ggc Gly 360	aac Asn	ata Ile	cct Pro	gtc Val	ttc Phe 365	gtt Val	att Ile	aat Asn	tat Tyr	cca Pro 370	1219
tta Leu	aca Thr	ctc Leu	aag Lys	cct Pro 375	ttc Phe	tac Tyr	atg Met	agg Arg	gat Asp 380	aat Asn	gaa Glu	gat Asp	ggc Gly	cct Pro 385	cag Gln	1267
cac His	acg Thr	gtt Val	gct Ala 390	gct Ala	gtt Val	gat Asp	ctt Leu	ctg Leu 395	gtt Val	cct Pro	gga Gly	gtt Val	999 Gly 400	gaa Glu	ctc Leu	1315
ttt Phe	gga Gly	gga Gly 405	ggc Gly	ctc Leu	aga Arg	gaa Glu	gaa Glu 410	cga Arg	tac Tyr	cat His	ttc Phe	tta Leu 415	gag Glu	gag Glu	cgc Arg	1363
tta Leu	gcc Ala 420	Arg	tat Tyr	ctg Leu	gac Asp	ctt Leu 425	cgt Arg	cga Arg	ttt Phe	gga Gly	tct Ser 430	gtg Val	cca Pro	cat His	gga Gly	1411
ggt Gly 435	ttt Phe	gjà aaa	atg Met	gga Gly	ttt Phe 440	gaa Glu	cgc Arg	tac Tyr	ctg Leu	cag Gln 445	tgc Cys	atc Ile	ttg Leu	ggt Gly	gtt Val 450	1459
gac Asp	aat Asn	atc Ile	aaa Lys	gat Asp 455	gtt Val	atc Ile	cct Pro	ttc Phe	cca Pro 460	agg Arg	ttt Phe	cct Pro	cat His	tca Ser 465	tgc Cys	1507
	tta Leu		ctg	gaag	att	ggtt	aag (	gaaa	agca	cc c	ccca	tggc	a ga	gaca	ctgc	1563
aca	tgat	tgt	gcat	acag	ca g	aatg	catg	t tt	ggat	ttta	gaa	atgo	aga	tttc	aatatg	1623
taa	ttgt	tgt	gcca	taag	at a	tcat	agaa	a aa	atat	aagt	ggt	tgtg	att	ttct	tagaaa	1683
gtt	gagg	gta	tttc	acgt	aa g	gatg	agct	c cc	gcaa	gaag	agg	tact	tat	agca	agggga	1743
ctc	tcaa	atc	catt	acct	ca a	ttaa	gaaa	t ga	agaa	attg	aat	tagt	ctc	aaag	tttctt	1803
tta	aact	cta	aaac	agaa	tg a	gata	atgt	a tt	ttac	gttg	tct	ataa	tca	ttaa	atcact	1863
ccc	tgtg	rtaa	tttg	rtgag	aa c	cato	tagt	a go	tcga	aata	aaa	taat	gtt	gcat	cttttc	1923
tcc	cttg	ıcca	tata	cttt	gt g	ataa	atco	t ta	tctc	attt	tca	gtac	ttc	atta	aacatt	1983
gca	ıgaaa	aaa	atat	tcct	ta a	ggto	ttaa	t tg	attt	aaag	aag	tago	tat	tctg	aattga	2043
aat	ctcc	ettt	catt	gaac	tg g	atga	aaaa	a to	atgt	ttaa	taa	ctgt	tgc	tttt	caatt	2103
tca	aago	etgt	tgag	gatat	ta c	atta	agta	t tt	caac	tctt	taa	tcac	etgt	tgtt	ataatt	2163
tgt	ttat	att	tgat	gttt	at a	attt	gtct	a at	.aaaa	taga	ttt	tttt	aat	agaa	aaaaaa	2223
aaa	ì															2226

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														_		••••
Tyr	Val	Ile	Tyr 200	Phe	Thr	Lys	Leu	Leu 205	Gly	Ser	Pro	Glu	Ser 210	Thr	Lys	
					_					_	-			aat Asn		785
														act Thr		833
														ggc		881
														cag Gln 275		929
gtg Val	tat Tyr	gat Asp	ata Ile 280	gtg Val	aat Asn	aat Asn	ctt Leu	ggc Gly 285	tcc Ser	ctt Leu	gtg Val	gcc Ala	aga Arg 290	tta Leu	att Ile	977
														gtg Val		1025
														gct Ala		1073
Ala 325	Ala	Ala	Val	Leu	Glu 330	Ser	Leu	Leu	Lys	Leu 335	Ala	Leu	Leu	gcc Ala	Gly 340	1121
														ctg Leu 355		1169
atc Ile	tac Tyr	gga Gly	360 GJA aaa	acc Thr	atg Met	ctt Leu	agc Ser	tca Ser 365	gga Gly	tcc Ser	ggt Gly	cct Pro	gtt Val 370	ttg Leu	ctg Leu	1217
														gtg Val		1265
gag Glu	tgt Cys 390	ttc Phe	aca Thr	ttt Phe	gct Ala	gcc Ala 395	atg Met	agc Ser	aaa Lys	gag Glu	gag Glu 400	gtc Val	gac Asp	agg Arg	tac Tyr	1313
aat Asn 405	ttt Phe	gtg Val	atg Met	ctg Leu	gcc Ala 410	ctg Leu	tcc Ser	tcc Ser	tca Ser	ttc Phe 415	ctg Leu	gtg Val	tta Leu	tcc Ser	tat Tyr 420	1361
ctc Leu	ttg Leu	acc Thr	cgt Arg	tgg Trp 425	tgt Cys	ggc	agc Ser	gtg Val	ggc Gly 430	ttc Phe	atc Ile	ttg Leu	gcc Ala	aac Asn 435	tgc Cys	1409
ttt Phe	aac Asn	atg Met	ggc Gly 440	att Ile	cgg Arg	atc Ile	acg Thr	cag Gln 445	agc Ser	ctt Leu	tgc Cys	ttc Phe	atc Ile 450	cac His	cgc Arg	1457
tac	tac	cga	agg	agc	ccc	cac	agg	ccc	ctg	gct	ggc	ctg	cac	cta	tcg	1505

Tyr Tyr Arg Arg Ser Pro His Arg Pro Leu Ala Gly Leu His Leu Ser 460 455 1553 cca qtc ctg ctc ggg aca ttt gcc ctc agt ggt ggg gtt act gct gtt Pro Val Leu Leu Gly Thr Phe Ala Leu Ser Gly Gly Val Thr Ala Val 475 470 tog gag gta tto ctc tgc tgt gag cag ggc tgg cca gcc aga ctg gca 1601 Ser Glu Val Phe Leu Cys Cys Glu Gln Gly Trp Pro Ala Arg Leu Ala 490 495 cac att gct gtg ggg gcc ttc tgt ctg gga gca act ctc ggg aca gca 1649 His Ile Ala Val Gly Ala Phe Cys Leu Gly Ala Thr Leu Gly Thr Ala ttc ctc aca gag acc aag ctg atc cat ttc ctc agg act cag tta ggt 1697 Phe Leu Thr Glu Thr Lys Leu Ile His Phe Leu Arg Thr Gln Leu Gly gtg ccc aga cgc act gac aaa atg acg tga c ttcagggaag cctggacacc 1748 Val Pro Arg Arg Thr Asp Lys Met Thr \* 1808 cgaggcacct ggaccageta tgggtagttc tgtgggtgga acacattctg tgtaagagcc ccactgaggg ctctgcagcg gagtgacagc aaccccagag atgaggcacc agagagtgcc 1868 actgcatgag acacctgtga ccattcgaag tctgaaatgc gggggggag tttcattttt 1928 1988 aagtgaagac caaaagccct ttaaaaaataa tagtttttta tcattttata gtaaaaaaaa 1992 aaaa

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gcgcagtcgg gggcacgggg atg agc tca ggg gcc tct aga aag agc tgg 110

Met Ser Ser Gly Ala Ser Arg Lys Ser Trp

1 5 10

gac cct ggg aag ccc tgg cct cca gac tgg cca atc aca ggc agg aag 158
Asp Pro Gly Lys Pro Trp Pro Pro Asp Trp Pro Ile Thr Gly Arg Lys
25

atg aag gtt ctg tgg gct gcg ttg ctg gtc aca ttc ctg gca gga tgc 206 Met Lys Val Leu Trp Ala Ala Leu Leu Val Thr Phe Leu Ala Gly Cys 30 35 40

cag gcc aag gtg gag caa gcg gtg gag aca gag ccg gag ccc gag ctg
Gln Ala Lys Val Glu Gln Ala Val Glu Thr Glu Pro Glu Pro Glu Leu

50
55

WO 01/55437	PCT/US01/02623
WU 01/55457	PC.17US01702023

• •	0 0 2, 0															,001,0101
cgc Arg	cag Gln 60	cag Gln	acc Thr	gag Glu	tgg Trp	cag Gln 65	agc Ser	ggc	cag Gln	cgc Arg	tgg Trp 70	gaa Glu	ctg Leu	gca Ala	ctg Leu	302
			tgg Trp													350
			gag Glu													398
			gag Glu 110													446
			ctg Leu													494
			cag Gln													542
			cgc Arg													590
			acc Thr													638
			aag Lys 190													686
ctg Leu	gca Ala	gtg Val 205	tac Tyr	cag Gln	gcc Ala	gly aaa	gcc Ala 210	cgc Arg	gag Glu	ggc	gcc Ala	gag Glu 215	cgc Arg	ggc Gly	ctc Leu	734
agc Ser	gcc Ala 220	atc Ile	cgc Arg	gag Glu	cgc Arg	ctg Leu 225	gly aaa	ccc Pro	ctg Leu	gtg Val	gaa Glu 230	cag Gln	ggc Gly	ccg Pro	cgt Arg	782
			cac His												agc Ser 250	830
GJÀ aaa	ccc Pro	agg Arg	cct Pro	999 Gly 255	gcg Ala	agc Ser	ggc Gly	tgc Cys	gcg Ala 260	cgc Arg	gga Gly	tgg Trp	agg Arg	aga Arg 265	tgg Trp	878
			ccc Pro 270							tga *	agga	gcca	ggt	gggc	gga	929
ggtg	gegeg	ıcc a	agct	ggag	g ag	rcagg	ccca	gca	gata	cgc	ctgc	aggo	cg a	ggcc	ttcc	a 989
ggcd	egec	tc a	agag	gctg	g tt	cgag	cccc	tgg	tgga	aga	catg	cago	gg c	cagt	aaaa	c 1049
ccgg	gctg	gt g	gaga	aggt	g ca	ggct	gccg	tgg	gcac	cag	cgcc	gccc	ct g	tgcc	cago	g 1109
acaa	tcac	tg a	acgc	cgaa	ıg cc	tgca	gcca	tgc	gaco	cca	cgcc	acco	cg t	gcct	cctg	c 1169

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ttt Phe	tta Leu	gtg Val	cag Gln	aca Thr 80	agt Ser	ttt Phe	gtt Val	cca Pro	gat Asp 85	gaa Glu	tac Tyr	tgg Trp	cag Gln	tct Ser 90	ctt Leu	1132
gaa Glu	gtt Val	tca Ser	cat His 95	cac His	atg Met	gtt Val	ttc Phe	aat Asn 100	tat Tyr	ggt Gly	tat Tyr	ttg Leu	act Thr 105	tgg Trp	gaa Glu	1180
						agt Ser										1228
						ctt Leu 130										1276
						gcc Ala										1324
						atg Met										1372
						cag Gln										1420
						aac Asn										1468
						ttg Leu 210										1516
						gca Ala										1564
						ttg Leu				His						1612
						cta Leu										1660
act Thr	ttg Leu	agt Ser 270	ttg Leu	tct Ser	ctg Leu	atg Met	att Ile 275	gat Asp	cgt Arg	att Ile	ttt Phe	ttt Phe 280	ggc Gly	caa Gln	tgg Trp	1708
act Thr	ctg Leu 285	gtt Val	caa Gln	ttt Phe	aat Asn	ttt Phe 290	ttg Leu	aaa Lys	ttt Phe	aac Asn	gtg Val 295	ctg Leu	cag Gln	aac Asn	tgg Trp	1756
gga Gly 300	aca Thr	ttt Phe	tat Tyr	ggt Gly	tct Ser 305	cat His	cca Pro	tgg Trp	cac His	tgg Trp 310	tac Tyr	ttc Phe	agt Ser	caa Gln	gga Gly 315	1804
ttt Phe	cca Pro	gtt Val	atc Ile	ttg Leu 320	ggt Gly	act Thr	cac His	tta Leu	ccc Pro 325	ttc Phe	ttt Phe	att Ile	cat His	ggc Gly 330	tgc Cys	1852

	cta Leu	-		_	_					_				_		1900
	ctg Leu															1948
	cca Pro 365															1996
	ctg Leu															2044
	ttg Leu															2092
	gat Asp	_	_	_					_	_						2140
	tct Ser		_		_		_	_	-		_					2188
	tac Tyr 445	-		-		_				_	_			_	_	2236
_	cca Pro	_	_	_			-	_			_	-	-	_	•	2284
	tac Tyr									_				_	_	2332
_	tca Ser	_				_				-		_	-		_	2380
	agc Ser		Phe													2428
	cac His 525	Thr														2476
tat Tyr 540	gaa Glu	cgg Arg	aag Lys	tta Leu	aaa Lys 545	Gly	aaa Lys	ttc Phe	aac Asn	atg Met 550	aag Lys	atg Met	aaa Lys	ttc Phe	tga	2524
act	ttcc	tag	ataa	atta	ac a	ttgc	tggg	t gg	aaat	attc	aga	tgct	gct	taaa	tacttc	2584
ggt	aaac	act	gggt	aaga	tt c	atgg	aact	t ag	aaaa	aagc	tgt	atga	act :	gctt	taccaa	2644
ata	tcac	tac	tgag	gaaa	tg t	ataa	aata	c ca	cata	gtat	aaa	atta	cat	gtta	atacaa	2704
tgc	caga	ttt	taaa	taaa	ga c	cttt	agtt	t tc	ctca	caga	aạa	aaga	aaa .	aaaa	aaa	2761

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***	J U KI S	J40 /												_	0 - 1 0 - 1 - 1	
	gtg Val															683
gtg Val	cag Gln	gtg Val 210	ggc	tat Tyr	ggt Gly	atg Met	gct Ala 215	gca Ala	gly aaa	tac Tyr	acc Thr	atc Ile 220	ttc Phe	atc Ile	acc Thr	731
	ttc Phe 225															779
atg Met 240	atc Ile	atg Met	att Ile	GJA 333	atg Met 245	gtc Val	tcc Ser	ttt Phe	gly aaa	tca Ser 250	gga Gly	gcc Ala	ctc Leu	ctc Leu	ttg Leu 255	827
_	ttt Phe						_				_	_		-	_	875
_	ttt Phe	-				_				-		_	_			923
	ata Ile	_						_			_		_	_	-	971
	ttg Leu 305															1019
	cag Gln															1067
	ttt Phe				_	_					_			_		1115
	caa Gln	_		_					_					tga *	aga	1163
tgc	ttac	ctg	cagg	aact	ga a	aaca	tcag	с са	tggc	cagg	CCC	ccag	aag	acaa	aagaag	1223
gga	ccgg	gga	actg	gtga	cc t	aagc	aacc	c ac	tgct	t						1260

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Met Phe Leu Phe Leu
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ata Ile	tgg Trp	ggt Gly	aca Thr 25	gag Glu	tcc Ser	aaa Lys	ccc Pro	cac His 30	tcc Ser	cgg Arg	ccc Pro	tac Tyr	atg Met 35	gca Ala	ttc Phe		149
			tat Tyr														197
			aaa Lys													:	245
aat Asn 70	ata Ile	aaa Lys	gta Val	acc Thr	tta Leu 75	ggt Gly	gct Ala	cac His	aat Asn	atc İle 80	aag Lys	aaa Lys	caa Gln	gaa Glu	aac Asn 85	:	293
			atc Ile													:	341
aga Arg	gat Asp	tca Ser	cat His 105	ttt Phe	aat Asn	gac Asp	atc Ile	atg Met 110	ctc Leu	ctg Leu	aag Lys	ttg Leu	gaa Glu 115	cgc Arg	aaa Lys	;	389
			aat Asn													4	437
gac Asp	tgg Trp 135	gtg Val	aaa Lys	cct Pro	gly aaa	cag Gln 140	gtg Val	tgc Cys	aca Thr	gtg Val	gca Ala 145	ggt Gly	tgg Trp	gga Gly	cgc Arg	4	485
ttg Leu 150	gcc Ala	aat Asn	tgt Cys	act Thr	tcg Ser 155	tct Ser	aac Asn	aca Thr	ctt Leu	caa Gln 160	gaa Glu	gtg Val	aat Asn	cta Leu	gaa Glu 165	Ę	533
gtt Val	cag Gln	aaa Lys	ggc Gly	cag Gln 170	aag Lys	tgc Cys	caa Gln	gac Asp	atg Met 175	tcc Ser	gaa Glu	gac Asp	tac Tyr	aac Asn 180	gac Asp	9	81
tcc Ser	atc Ile	cag Gln	ctt Leu 185	tgt Cys	gtg Val	gga Gly	aac Asn	ccc Pro 190	agc Ser	gag Glu	gly ggg	aag Lys	gct Ala 195	act Thr	ggt Gly	6	529
aag Lys	gga Gly	gac Asp 200	tca Ser	gly ggg	ggt Gly	ccc Pro	ttt Phe 205	gtg Val	tgc Cys	gat Asp	gga Gly	atg Met 210	gcc Ala	cca Pro	gly aaa	6	57 <b>7</b>
cat His	tgg Trp 215	cag Gln	tta Leu	tcg Ser	gct Ala	tgg Trp 220	gta Val	ctg Leu	gga Gly	aca Thr	ctt Leu 225	tct Ser	cga Arg	gaa Glu	ttt Phe	7	725
ccc Pro 230	cag Gln	aat Asn	ctc Leu	cag Gln	ctt Leu 235	tta Leu	tac Tyr	cgg Arg	gga Gly	ttt Phe 240	aga Arg	aaa Lys	cca Pro	atg Met	aaa Lys 245	7	73
ggc Gly	cct Pro	taa *	caat	tcc	taga	aacc	ca a	aacc	ctgg	g to	ttgo	ggcc	aat	ggcc	cca	8	29

ccatccctgg gggaatgggg ttaatttgag ggcctcaaaa aagaaaaccc ttttcccgcc 889

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acatgtctag ggtctagac atg ttc agc ttt gtg gac ctc cgg ctc ctg ctc  Met Phe Ser Phe Val Asp Leu Arg Leu Leu  1 5 10														
ctc tta gcg gcc acc gcc ctc ctg acg cac ggc caa gag gaa ggc caa Leu Leu Ala Ala Thr Ala Leu Leu Thr His Gly Gln Glu Glu Gly Gln 15 20 25	220													
gtc gag ggc caa gac gaa gac atc cca cca atc acc tgc gta cag aac Val Glu Gly Gln Asp Glu Asp Ile Pro Pro Ile Thr Cys Val Gln Asn 30 35 40	268													
ggc ctc agg tac cat gac cga gac gtg tgg aaa ccc gag ccc tgc cgg Gly Leu Arg Tyr His Asp Arg Asp Val Trp Lys Pro Glu Pro Cys Arg 45 50 55	316													
atc tgc gtc tgc gac aac ggc aag gtg ttg tgc gat gac gtg atc tgt Ile Cys Val Cys Asp Asn Gly Lys Val Leu Cys Asp Asp Val Ile Cys 60 65 70 75	364													
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gga gga aac ttt gct ccc cag ctg tct tat ggc tat gat gag aaa tca Gly Gly Asn Phe Ala Pro Gln Leu Ser Tyr Gly Tyr Asp Glu Lys Ser	652													

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			ggt ccc caa ggc Gly Pro Gln Gly 200	
			gct tca ggt ccc Ala Ser Gly Pro 215	
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gga aaa cct Gly Lys Pro	ggt cgt cct Gly Arg Pro 240	ggt gag cgt Gly Glu Arg	ggg cct cct ggg Gly Pro Pro Gly 245	cct cag ggt 892 Pro Gln Gly 250
Ala Arg Gly			ctc cct gga atg Leu Pro Gly Met	
			aag gga gat gct Lys Gly Asp Ala 280	
ggt cct aag Gly Pro Lys 285	ggt gag cct Gly Glu Pro	ggc agc cct Gly Ser Pro 290	ggt gaa aat gga Gly Glu Asn Gly 295	gct cct ggt 1036 Ala Pro Gly
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gaa ggt ccc o Glu Gly Pro o 365	cag ggt gtg Gln Gly Val	cgt ggt gag Arg Gly Glu 370	cet ggc ccc cet g Pro Gly Pro Pro 375	ggc cct gct 1276 Gly Pro Ala
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			att gct ggt gct ( Ile Ala Gly Ala ! 405	
cct ggt gcc o	ega ggc ccc Arg Gly Pro	tct gga ccc Ser Gly Pro	cag ggc ccc ggc o Gln Gly Pro Gly o	ggc cct cct 1420 Gly Pro Pro

415 420 425

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cct Pro 460	ggc Gly	cct Pro	gct Ala	gga Gly	gag Glu 465	gaa Glu	gga Gly	aag Lys	cga Arg	gga Gly 470	gct Ala	cga Arg	ggt Gly	gaa Glu	ecc Pro 475	1564
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Leu 540		Gly	Ser	Pro	Gly 545	Ser	Pro	Gly	Pro	Asp 550	Gly	Lys	Thr	GIY	555	1804
ect	ggt Gly	ecc Pro	gcc Ala	ggt Gly 560	Gln	gat Asp	ggt Gly	cgc Arg	ccc Pro 565	Gly	ccc Pro	cca Pro	ggc	Pro 570	Pro	1852
ggt	gcc Ala	cgt Arg	ggt Gly 575	gln Gln	gct Ala	ggt Gly	gtg Val	atg Met 580	Gly	ttc Phe	cct Pro	gga Gly	CCt Pro 585	Lys	ggt	1900
gct Ala	get Ala	gga Gly 590	y Glu	p ccc	ggc Gly	aag Lys	gct Ala 595	Gly	gag Glu	cga Arg	ggt Gly	gtt Val 600	Pro	gga Gly	Pro	1948
Pro	605 605	/ Ala	t gto a Val	ggt LGly	cct Pro	gct Ala 610	Gly	aaa / Lys	gat Asp	gga Gl	gag Glu 619	ı Ala	gga Gly	gct Ala	cag Gln	1996
gg: Gl: 62	y Pro	o Pro	t ggd o Gly	e ect y Pro	get Ala 625	ı Gly	Pro	c gct o Ala	ggo Gly	gag Glu 630	ı Arç	a ggt g Gly	gaa Glu	a caa a Glr	ggc Gly 635	2044
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cc Pr	a gg o Gl	t ga y Gl	a gca u Ala 659	a Gly	c aaa y Lys	a cct s Pro	gg(	t gaa y Gli 660	ı Glı	g ggt n Gly	t gti y Val	t cct	gg 66!	y Ası	c ctt p Leu	2140
G1	c gc	c cc a Pr	t gg o Gl	c cc	c tc	gga Gly	a.gca / Ala	a aga a Arg	a ggo	gag y Gl	g aga	a ggi g Gl	t tto y Pho	e cc	ggc Gly	2188

670 . 675 . 680

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Ala	Gly	ccc Pro 750	Lys	Gly	Ala	qaA	Gly 755	Ser	Pro	Gly	Lys	760	Gly	Val	Arg	2428
Gly	Leu 765	acc Thr	Gly	Pro	Ile	Gly 770	Pro	Pro	Gly	Pro	Ala 775	Gly	Ala	Pro	Gly	2476
gac Asp 780	aag Lys	ggt Gly	gaa Glu	agt Ser	ggt Gly 785	ccc Pro	agc Ser	ggc Gly	cct Pro	gct Ala 790	ggt Gly	ccc Pro	act Thr	gga Gly	gct Ala 795	2524
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		gct Ala														2620
		ggt Gly 830														2668
gcc Ala	gga Gly 845	ccc Pro	gct Ala	gga Gly	ccc Pro	cct Pro 850	ggc Gly	ccc Pro	att Ile	ggt Gly	aat Asn 855	gtt Val	ggt Gly	gct Ala	cct Pro	2716
		aaa Lys														2764
		ggt Gly														2812
-		ccc Pro							_			-				2860
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		ggt Gly					-								-	2956

925 930 935

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gga Gly	cag Gln	cgt Arg	ggt Gly	gtg Val 960	gtc Val	ggc	ctg Leu	cct Pro	ggt Gly 965	cag Gln	aga Arg	gga Gly	gag Glu	aga Arg 970	ggc Gly	:	3052
ttc Phe	cct Pro	ggt Gly	ctt Leu 975	cct Pro	ggc Gly	ccc Pro	tct Ser	ggt Gly 980	gaa Glu	cct Pro	ggc Gly	aaa Lys	caa Gln 985	ggt Gly	ccc Pro	;	3100
tct Ser	gga Gly	gca Ala 990	agt Ser	ggt Gly	gaa Glu	cgt Arg	ggt Gly 995	ccc Pro	cct Pro	ggt Gly	Pro	atg Met L000	ggc Gly	ccc Pro	cct Pro	;	3148
	ttg Leu 1005				Pro					Arg							3196
gcc Ala 1020	gaa Glu	ggt Gly	tcc Ser	Pro	gga Gly 1025	cga Arg	gac Asp	ggt Gly	Ser	cct Pro 1030	ggc Gly	gcc Ala	aag Lys	Gly	gac Asp 1035		3244
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	gcc Ala	Pro					Pro					Gly					3340
	g act 1 Thr		Pro			Pro					Gly						3388
_	g ggc g Gly 1085	Pro	_		Pro		Gly		_	Gly							3436
gg( Gl <sub>)</sub> 1100	e gaa y Glu )	cag Gln	ggc	Asp	aga Arg 1105	Gly	ata Ile	aag Lys	Gly	cac His 1110	Arg	ggc	ttc Phe	tct Ser	ggc Gly 1115		3484
	c cag ı Gln				Gly			Gly		Pro					Pro		3532
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	t gct y Ala		Gly		_			Asn			Pro		Pro				3628
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ttc gac ttc agc ttc ctg ccc cag cca cct caa gag aag gct c Phe Asp Phe Ser Phe Leu Pro Gln Pro Pro Gln Glu Lys Ala F 1200 1205	ac gat 3772 His Asp 210
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gac ctc gag gtg gac acc acc ctc aag agc ctg agc cag cag Asp Leu Glu Val Asp Thr Thr Leu Lys Ser Leu Ser Gln Gln I 1230 1235 1240	atc gag 3868 (le Glu
aac atc cgg agc cca gag ggc agc cgc aag aac ccc gcc cgc a Asn Ile Arg Ser Pro Glu Gly Ser Arg Lys Asn Pro Ala Arg 1 1245 1250 1255	acc tgc 3916 Thr Cys
cgt gac ctc aag atg tgc cac tct gac tgg aag agt gga gag t Arg Asp Leu Lys Met Cys His Ser Asp Trp Lys Ser Gly Glu 1 1260 1265 1270	ac tgg 3964 Tyr Trp 1275
att gac ccc aac caa ggc tgc aac ctg gat gcc atc aaa gtc t Ile Asp Pro Asn Gln Gly Cys Asn Leu Asp Ala Ile Lys Val I 1280 . 1285 12	ete tgc 4012 Phe Cys 290
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gcc cag aag aac tgg tac atc agc aag aac ccc aag gac aag a Ala Gln Lys Asn Trp Tyr Ile Ser Lys Asn Pro Lys Asp Lys A 1310 1315 1320	agg cat 4108 Arg His
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cgc ctg atg tcc acc gag gcc tcc cag aac atc acc tac cac Arg Leu Met Ser Thr Glu Ala Ser Gln Asn Ile Thr Tyr His c 1360 1365 1	tgc aag 4252 Cys Lys 370
aac agc gtg gcc tac atg gac cag cag act ggc aac ctc aag a Asn Ser Val Ala Tyr Met Asp Gln Gln Thr Gly Asn Leu Lys 1 1375 1380 1385	aag gcc 4300 Lys Ala
ctg ctc ctc cag ggc tcc aac gag atc gag atc cgc gcc gag g Leu Leu Leu Gln Gly Ser Asn Glu Ile Glu Ile Arg Ala Glu ( 1390 1395 1400	ggc aac 4348 Gly Asn
age ege tte ace tae age gte act gte gat gge tge acg agt of Ser Arg Phe Thr Tyr Ser Val Thr Val Asp Gly Cys Thr Ser 1405 1410 1415	
gga gcc tgg ggc aag aca gtg att gaa tac aaa acc acc aag Gly Ala Trp Gly Lys Thr Val Ile Glu Tyr Lys Thr Thr Lys 1420 1425 1430	
cgc ctg ccc atc atc gat gtg gcc ccc ttg gac gtt ggt gcc Arg Leu Pro Ile Ile Asp Val Ala Pro Leu Asp Val Gly Ala	cca gac 4492 Pro Asp

1440 1445 1450

cag gaa ttc ggc ttc gac gtt ggc cct gtc tgc ttc ctg taaactccct Gln Glu Phe Gly Phe Asp Val Gly Pro Val Cys Phe Leu 1455 1460	4541
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gat Asp	cct Pro	gtc Val	ctg Leu	gcc Ala 125	aag Lys	gtg Val	gca Ala	ggt Gly	gac Asp 130	tgc Cys	ttg Leu	gat Asp	gag Glu	aag Lys 135	cag Gln	1037
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				gcc Ala 205												1277
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Atg acc cag aac tac cag gac tca cca acc ctc cag gct ccc aga gga Met Thr Gln Asn Tyr Gln Asp Ser Pro Thr Leu Gln Ala Pro Arg Gly 200 205 210	800
agg gcc agc gag ccc aag cac aaa acc agg cag aga tag ctgcctgcta Arg Ala Ser Glu Pro Lys His Lys Thr Arg Gln Arg * 215 220	849
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cga cgc tcc ttc tgg act gta atg cgc act gcg tgg aga tgt tcg tgt 164
Arg Arg Ser Phe Trp Thr Val Met Arg Thr Ala Trp Arg Cys Ser Cys

10

Met

tcc agt gta gac agg gcg ttg tca cat cag gca gga cta cag gga caa

212

Ser Ser Val Asp Arg Ala Leu Ser His Gln Ala Gly Leu Gln Gly Gln

20

25

30

tgt ttg tca gcc tgt ctt ctg ggc aac ttg ggg tat cct ccc ttt ata 260
Cys Leu Ser Ala Cys Leu Leu Gly Asn Leu Gly Tyr Pro Pro Phe Ile
.35 40

tea cet cet gee cag gtg ete tge gee gee aga gea tea tgt eat ttg

Ser Pro Pro Ala Gln Val Leu Cys Ala Ala Arg Ala Ser Cys His Leu

50 65

gga toc ctg atg gca att ttg aga ctt tgg ttc aca gta aag att ggt 356 Gly Ser Leu Met Ala Ile Leu Arg Leu Trp Phe Thr Val Lys Ile Gly 70 75 80

cct gtg tga tcttaaa gtaatgtggc ttaaaaacaa atggctgtca gggaattgta 412 Pro Val \*

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24

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<210> 11

<211> 2779

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<213> Homo sapiens

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ctt Leu	gca Ala 170	atc Ile	gtt Val	gga Gly	gjå aaa	ggc Gly 175	tat Tyr	act Thr	cca Pro	tcc Ser	aaa Lys 180	tat Tyr	gca Ala	gtg Val	gaa Glu	1959
ggt Gly 185	ttc Phe	aat Asn	gac Asp	agc Ser	tta Leu 190	aga Arg	cgg Arg	gac Asp	atg Met	aaa Lys 195	gct Ala	ttt Phe	ggt Gly	gtg Val	cac His 200	2007
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gta Val	aag Lys	gta Val	att Ile 220	gaa Glu	aaa Lys	aaa Lys	ctc Leu	gcc Ala 225	att Ile	tgg Trp	gag Glu	cag Gln	ctg Leu 230	tct Ser	cca Pro	2103

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Phe Ser Val Ser 35	Pro Gly Gly 40	Thr Val Thr I	Leu Thr Cys Gly I 45	Leu Asn
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	Asp Arg Phe		atc gtt ggg aac a Ile Val Gly Asn I 95	
			yat gag tgt gtt t Asp Glu Cys Val I 110	
			etg ttc ggc gga g Seu Phe Gly Gly G 125	
aga ctg acc gtc Arg Leu Thr Val 130	cta ggt cag Leu Gly Gln 135	Pro Lys Ala A	gcc ccc tcg gtc a Ala Pro Ser Val I 140	ct ctg 488 Chr Leu 145
			ac aag gcc aca c Asn Lys Ala Thr I 1	
	Asp Phe Tyr		ytg aca gtg gcc t Val Thr Val Ala T 175	
			gag acc acc aca c Glu Thr Thr Thr F 190	
aaa caa agc aac Lys Gln Ser Asn 195	aac aag tac Asn Lys Tyr 200	gcg gcc agc a	gc tac ctg agc c Ser Tyr Leu Ser L 205	etg acg 680 eu Thr
cct gag cag tgg Pro Glu Gln Trp 210	aag tcc cac Lys Ser His 215	Lys Ser Tyr S	ngc tgc cag gtc a Ser Cys Gln Val T 220	cg cat 728 Thr His 225
gaa ggg agc acc Glu Gly Ser Thr	gtg gag aag Val Glu Lys 230	aca gtg gcc of Thr Val Ala E 235	ect aca gaa tgt t Pro Thr Glu Cys S 2	ca tag 776 er * 40
gttcccaact ctaa	ccccac ccacg	ggagc ctggagct	gc aggateceag gg	gaggggt 836
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gag Glu 165	ı Val	g gtg . Val	g ccc L Pro	aga Arg	1 ggg 1 Gly 170	, Gly	tcg Ser	g gtg : Val	g tco Ser	Glr 175	ı Arç	g Gly	ago Ser	: ato	ggc Gly 180	1003
ago Ser	cac His	cag Glr	g agt 1 Ser	gto Val	. Arg	gtg Val	gtg Val	g cac His	aga Arg	Thr	cag Glr	g ago Ser	acc Thr	aag Lys 199	tcc Ser	1051
cac	cgg Arg	r cgc	Thr	Gly	agc Ser	cgg	gcc	gag Glu 205	Ala	aag Lys	g agg S Arg	gcc Ala	ago Ser 210	Met	ctg Leu	1099
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gag Glu	ctg Leu	aag Lys 295	tcc Ser	ccg Pro	gtg Val	aag Lys	acg Thr 300	ata Ile	gaa Glu	gac Asp	ttc Phe	ctg Leu 305	cgg Arg	agg Arg	ttc Phe	1387
aca Thr	ccc Pro 310	agc Ser	tgc Cys	ctg Leu	acc Thr	tca Ser 315	ggc Gly	tgc Cys	agc Ser	agc Ser	atc Ile 320	Gly aaa	agc Ser	ctg Leu	gcc Ala	1435
gcc Ala 325	aac Asn	aag Lys	tcc Ser	agc Ser	cac His 330	aag Lys	ttg Leu	ggc Gly	tcc Ser	agc Ser 335	ttc Phe	ccg Pro	tcc Ser	acc Thr	ccg Pro 340	1483
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gcc Ala	tcg Ser	gag Glu 375	ctt Leu	gct Ala	cag Gln	gag Glu	cag Gln 380	gag Glu	tca Ser	gag Glu	cgc Arg	gag Glu 385	ctg Leu	cgg Arg	tac Tyr	1627
gag Glu	gcg Ala 390	gag Glu	agc Ser	ccg Pro	Asp	gag Glu 395	gcc Ala	gca Ala	ctg Leu	gtg Val	tat Tyr 400	gcg Ala	gcc Ala	aga Arg	gcc Ala	1675
tac Tyr 405	aac Asn	tgc Cys	gtg Val	Leu	gtg Val 410	gag Glu	cgg Arg	ctg Leu	His	gac Asp 415	caa Gln	gtg Val	tca Ser	gtg Val	gag Glu 420	1723

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	_		_	cgc Arg	_									_		1819
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				agc Ser												1963
				acc Thr 505												2011
Glu	Tyr	Ala	Cys 520	tgg Trp	Leu	Gln	Ser	His 525	Leu	Glu	Ala	Glu	Ser 530	Ser	Leu	2059
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	_		-	tta Leu		_				_	_	-	_	_	_	2155
				act Thr											att Ile 580	2203
-	_			ggt Gly 585	-	•		-		_	_			_		2251
_	_		_	ctg Leu	-		_			_			_		_	2299
		_		gcg Ala	_	_	_	_		-	_	_		-		2347
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	_	-		ttc Phe				_				•			_	2443
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		Leu				_	Ser			_	_	Phe				acc Thr 900	3163
				, aca Thr		Ala	_				Leu					Ile	3211
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WC	01/5	5437												1	PCT/US	501/02623
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											atg Met 960					3355
											acg Thr					3403
											Gly ggg					3451
		Leu					Gln				aag Lys	Ser				3499
	Ser					Thr					cgc Arg					3547
Ser					Ser					۷al	aag Lys 1040					3595
				Ser					Gln		gtc Val			Leu		3643
_	_		Glu		_			Asp	_	_	atg Met		Val			3691
		Leu	_			_	Ser	_	-	-	ccc Pro	Met				3739
	Gly	-	-	_	_	Arg	_				tgt Cys			-		3787
Lys					Ser					Thr	ccc Pro 1120					3835
	-	_		Thr		_			Asn		att Ile			Trp	_	3883
			Arg					Leu			tcc Ser		Thr			3931
		Asp					Arg				gtc Val	Gln				3979
	Arg					Gly		_		_	cta Leu				•	4027

tet tea agg egg tea eag tga aa acettgaaat ggeetttttt aatatatata 4080 Ser Ser Arg Arg Ser Gln \* aataaatgtt aatattattt atgtttatta tttgcacaga agagttctag ggagatgtat 4140 ttctaaatgt ttcccaggct aatacaggaa acaagaggta ccaaaaaaga aagtttattt 4200 tttaaaattc taagtagagt atattgaaaa gaaaaagaag agccttaaca tatataaaag 4260 tttaaagaag agtaacactt gaaaagtgtg tttagattta ttttttcatc tcatttttaa 4320 gaacaagcag tacgatttgt tttcttcaac atgtgtgact gcgcactgag tacaaatgtg 4380 tgactgctca tggttaatgc aggcaggtgt gaacatgggg gaacaatgag cagagatggc 4440 agagggcaga gcacatggcc cccagaggct tccagtctca ctgacacagg agggctgggc 4500 tccacttcat ccagatgaag gaaaggaaga cctcaagaaa aattcacagt tgagtgcatc 4560 ccagcattct gttccgggca ggcatttcag gaagaccgcc ttgtaggtat tacatccctg 4620 gtgtcgtatt ttgcctgtta aatcgtaaca agcaataaac aactttcact ttgcaaagac 4680 agtgtgtcca gttaccactg gtgtatgaaa tgattaatac ctgacctcac agagtatgat 4740 ctgagggcac ttccgtaagg caagtccttt tagaggctat gaagaaaaca gctgcatggc 4800 acataccaaa getgetgeac ageeggeeac catggeacce tgeaccagge cateaqeacc 4860 acgtgccaag gagctcagcg gtcttcaggc atttttgtaa tgagccatta gttctgtccc 4920 tctaaaacta gaaaaggaag ggcaggaaat gataacaacc caaggcaatg atatggcatg 4980 tcatcttctg agccettctt tctactttgt caaacagttc ttagttgctg gctctgctcg 5040 gcaccggggc tgtgaagggt gtactccctg ctgtgtggga gggacctagg gcctctttgg 5100 atgctgtctt cgaggacagc aatgcagaga gggcatagga tctgaggaca aggaaattcc 5160 teageatgge gtateaggaa ageatggete attetgeaat qaqeeatgaq tqtqqqeeat 5220 cgcaagtcac agaaattgca cctcattcca gtcaagcaga aaaacaggca caggctcagt 5280 gtaggtccca agagaggtg cctggactca gcaactcgga cctgggcttt tctcccagct 5340 ttcagggaca gctttgtcct gagtctgcct ctgttcacgg ggatgcttgg ctggagtcac 5400 ccccaggact tatccatgca tcactattca gaagacacag agggcccctc tctccacatt 5460 ccaaacagag tcctggtttc ctcagcctca ccctgcatag cttgcacaac atcctcagaa 5520 ccattcactg gcaaatggag gggaacgtgc tgactgggac tcccagctgg agctgggagg 5580 agaggtecae tteeettaga acaeetgage tgetgeatga gtggaegtea gaagaatete 5640 tatgccctgt taaatgggga gacaaagggg tggtgggggc ttcagccagt gatttcggac 5700 cgaaggtgac agccgtccca accctgccca gcctgatgcc acctcctctg ttcttggaac 5760 aacgcatagg aaaagaatet eetttggaag gtgacaetge teeetgaatt aaggtaatgg 5820 ttgcgagcac caagtacaag gactagacgc atatttacct gcgtatctga gagttccaga 5880

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105

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737

act agt gcc aag ctc tca gtg ctc gaa gag gaa cag ctg ccc cct ggg

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						999 Gly 140										785
						tgt Cys										833
				_	_	ttc Phe			_	_		-	_	-		881
ggc	cgc Arg	atc Ile	aag Lys 185	cag Gln	ctg Leu	cgt <b>Ar</b> g	tca Ser	ggt Gly 190	gcc Ala	ttg Leu	cag Gln	ata Ile	gag Glu 195	agc Ser	agt Ser	929
						aag Lys										977
ggc Gly	aca Thr 215	cgt Arg	tac Tyr	tca Ser	gcc Ala	cct Pro 220	gcg Ala	aac Asn	ctg Leu	tat Tyr	gtg Val 225	cga Arg	gtg Val	cgc Arg	cgc Arg	1025
						atc Ile										1073
						aca Thr										1121
tac Tyr	gtg Val	aag Lys	tgg Trp 265	atg Met	atg Met	Gly 333	gcc Ala	gag Glu 270	gag Glu	ctc Leu	acc Thr	aag Lys	gag Glu 275	gat Asp	gag Glu	1169
atg Met	cca Pro	gtt Val 280	ggc Gly	cgc Arg	aac Asn	gtc Val	ctg Leu 285	gag Glu	ctc Leu	agc Ser	aat Asn	gtc Val 290	gta Val	cgc Arg	tct Ser	1217
gcc Ala	aac Asn 295	tac Tyr	acc Thr	tgt Cys	gtg Val	gcc Ala 300	atc Ile	tcc Ser	tcg Ser	ctg Leu	ggc Gly 305	atg Met	atc Ile	gag Glu	gcc Ala	1265
aca Thr 310	gcc Ala	cag Gln	gtc Val	aca Thr	gtg Val 315	aaa Lys	gct Ala	ctt Leu	cca Pro	aag Lys 320	cct Pro	ccg Pro	att Ile	gat Asp	ctt Leu 325	1313
gtg Val	gtg Val	aca Thr	gag Glu	aca Thr 330	act Thr	gcc Ala	acc Thr	agt Ser	gtc Val 335	acc Thr	ctc Leu	acc Thr	tgg Trp	gac Asp 340	tct Ser	1361
Gly 999	aac Asn	tcg Ser	gag Glu 345	cct Pro	gta Val	acc Thr	tac Tyr	tat Tyr 350	ggc Gly	atc Ile	cag Gln	tac Tyr	cgc Arg 355	gca Ala	gcg Ala	1409
ggc Gly	acg Thr	gag Glu 360	ggc Gly	ccc Pro	ttt Phe	cag Gln	gag Glu 365	gtg Val	gat Asp	ggt Gly	gtg Val	gcc Ala 370	acc Thr	acc Thr	cgc Arg	1457
tac	agc	att	ggc	ggc	ctc	agc	cct	ttc	tcg	gaa	tat	gcc	ttc	cgc	gtg	1505

WC	01/5	5437												1	2C 17U	501/02023
Tyr	Ser 375	Ile	Gly	Gly	Leu	Ser 380	Pro	Phe	Ser	Glu	Tyr 385	Ala	Phe	Arg	Val	
ctg Leu 390	gcg Ala	gtg Val	aac Asn	agc Ser	atc Ile 395	gly ggg	cga Arg	Gly 999	ccg Pro	ccc Pro 400	agc Ser	gag Glu	gca Ala	gtg Val	cgg Arg 405	1553
gca Ala	cgc Arg	acg Thr	gga Gly	gaa Glu 410	cag Gln	gcg Ala	ccc Pro	tcc Ser	agc Ser 415	cca Pro	ccg Pro	cgc Arg	cgc Arg	gtg Val 420	cag Gln	1601
gca Ala	cgc Arg	atg Met	ctg Leu 425	agc Ser	gcc Ala	agc Ser	acc Thr	atg Met 430	ctg Leu	gtg Val	cag Gln	tgg Trp	gag Glu 435	cct Pro	ccc Pro	1649
gag Glu	gag Glu	ccc Pro 440	aac Asn	ggc Gly	ctg Leu	gtg Val	cgg Arg 445	gga Gly	tac Tyr	cgc Arg	gtc Val	tac Tyr 450	tat Tyr	act Thr	ccg Pro	1697
gac Asp	tcc Ser 455	cgc Arg	cgc Arg	ccc Pro	ccg Pro	aac Asn 460	gcc Ala	tgg Trp	cac His	aag Lys	cac His 465	aac Asn	acc Thr	gac Asp	gcg Ala	1745
999 Gly 470	ctc Leu	ctc Leu	acg Thr	acc Thr	gtg Val 475	ggc Gly	agc Ser	ctg Leu	ctg Leu	cct Pro 480	ggc	atc Ile	acc Thr	tac Tyr	agc Ser 485	1793
					ttc Phe											1841
					acg Thr											1889
ttc Phe	cag Gln	gcc Ala 520	gag Glu	gtg Val	gag Glu	tcg Ser	gac Asp 525	acc Thr	agg Arg	atc Ile	cag Gln	ctc Leu 530	tcg Ser	tgg Trp	ctg Leu	1937
ctg Leu	ccc Pro 535	cct Pro	cag Gln	gag Glu	cgg Arg	atc Ile 540	atc Ile	atg Met	tat Tyr	gaa Glu	ctg Leu 545	gtg Val	tac Tyr	tgg Trp	gcg Ala	1985
gca Ala 550	gag Glu	gac Asp	gaa Glu	gac Asp	caa Gln 555	cag Gln	cac His	aag Lys	gtc Val	acc Thr 560	ttc Phe	gac Asp	cca Pro	acc Thr	tcc Ser 565	2033
tcc Ser	tac Tyr	aca Thr	cta Leu	gag Glu 570	gac Asp	ctg Leu	aag Lys	cct Pro	gac Asp 575	aca Thr	ctc Leu	tac Tyr	cgc Arg	ttc Phe 580	cag Gln	2081
					gat Asp											2129
					cag Gln											2177
atg Met	tgt Cys 615	gtg Val	agc Ser	atg Met	ggc Gly	tcc Ser 620	acc Thr	acg Thr	gtc Val	cgg Arg	gta Val 625	agt Ser	tgg Trp	gtc Val	ccg Pro	2225
ccg	cct	gcc	gac	agc	cgc	aac	ggc	gtt	atc	acc	cag	taċ	tcc	gtg	gcc	2273

WC	01/5	5437												F	PCT/US	801/02623
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atc Ile	agc Ser	cgt Arg	gag Glu 665	cac His	tcc Ser	agc Ser	tgg Trp	gac Asp 670	ctg Leu	gtg Val	ggc Gly	ctg Leu	gag Glu 675	aag Lys	tgg Trp	2369
acg Thr	gag Glu	tac Tyr 680	cgg Arg	gtg Val	tgg Trp	gtg Val	cgg Arg 685	gca Ala	cac His	aca Thr	gac Asp	gtg Val 690	ggc Gly	ccc Pro	ggc Gly	2417
ccc Pro	gag Glu 695	agc Ser	agc Ser	ccg Pro	gtg Val	ctg Leu 700	gtg Val	cgc Arg	acc Thr	gat Asp	gag Glu 705	gac Asp	gtg Val	ccc Pro	agc Ser	2465
ggg Gly 710	cct Pro	ccg Pro	cgg Arg	aag Lys	gtg Val 715	gag Glu	gtg Val	gag Glu	cca Pro	ctg Leu 720	aac Asn	tcc Ser	act Thr	gct Ala	gtg Val 725	2513
cat His	gtc Val	tac Tyr	tgg Trp	aag Lys 730	ctg Leu	cct Pro	gtc Val	ccc Pro	agc Ser 735	aag Lys	cag Gln	cat His	ggc Gly	cag Gln 740	atc Ile	2561
cgc Arg	ggc Gly	tac Tyr	cag Gln 745	gtc Val	acc Thr	tac Tyr	gtg Val	cgg Arg 750	ctg Leu	gag Glu	aat Asn	ggc Gly	gag Glu 755	Pro	cgt Arg	2609
gga Gly	ctc Leu	ccc Pro 760	Ile	atc Ile	caa Gln	gac Asp	gtc Val 765	atg Met	cta Leu	gcc Ala	gag Glu	gcc Ala 770	Gln	tgg Trp	cgg Arg	2657
cca Pro	gag Glu 775	Glu	tcc Ser	gag Glu	gac Asp	tat Tyr 780	Glu	acc Thr	act Thr	atc Ile	agc Ser 785	ggc Gly	ctg Leu	acc Thr	ccg Pro	2705
gag Glu 790	Thr	acc Thr	tac Tyr	Ser	gtt Val 795	Thr	gtt Val	gct Ala	gcc Ala	tat Tyr 800	Thr	acc Thr	aag Lys	Gly	gat Asp 805	2753
ggt Gly	gcc Ala	cgc	ago Ser	aag Lys 810	Pro	aaa Lys	att Ile	gtc Val	act Thr 815	Thr	aca Thr	ggt	gca Ala	gto Val 820	cca Pro	2801
ggo	cgg Arg	Pro	acc Thr 825	Met	atg Met	atc Ile	agc Ser	tacc Thr	Thr	gcc	atg Met	aac Asn	act Thr 835	Ala	ctg Leu	2849
			His					Leu					Lev		tac Tyr	2897
		Glr					Asp					Asn			gat Asp	2945
tto Phe 870	e Gly	aag Lys	g gat s Asp	gac Asp	cag Gln 875	His	tto Phe	aca Thr	gto Val	acc Thr	Gly	cto Lev	g cac ı His	aag Lys	999 Gly 885	2993
aco	acc	: tac	ato	: tto	c cgg	, ctt	gct	gcc	aag	aac	cgg	gct	ggd	tte	g ggt	3041

WC	01/5	5437												ı	/C1/03	01/02023
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ttc Phe	ccc Pro	caa Gln 920	aac Asn	ctg Leu	cat His	gtg Val	aca Thr 925	gga Gly	ctg Leu	acc Thr	acg Thr	tct Ser 930	acc Thr	aca Thr	gaa Glu	3137
ctg Leu	gcc Ala 935	tgg Trp	gac Asp	ccg Pro	cca Pro	gtg Val 940	ctg Leu	gcg Ala	gag Glu	agg Arg	aac Asn 945	gly ggg	cgc Arg	atc Ile	atc Ile	3185
agc Ser 950	tac Tyr	acc Thr	gtg Val	gtg Val	ttc Phe 955	cga Arg	gac Asp	atc Ile	aac Asn	agc Ser 960	caa Gln	cag Gln	gag Glu	ctg Leu	cag Gln 965	3233
aac Asn	atc Ile	acg Thr	aca Thr	gac Asp 970	acc Thr	cgc Arg	ttt Phe	acc Thr	ctt Leu 975	act Thr	ggc Gly	ctc Leu	aag Lys	cca Pro 980	gac Asp	3281
acc Thr	act Thr	tac Tyr	gac Asp 985	atc Ile	aag Lys	gtc Val	cgc Arg	gca Ala 990	tgg Trp	acc Thr	agc Ser	aaa Lys	ggc Gly 995	tct Ser	ggc Gly	3329
cca Pro	Leu	agc Ser 1000	ccc Pro	agc Ser	atc Ile	Gln	tcc Ser 1005	Arg	acc Thr	atg Met	Pro	gtg Val 1010	gag Glu	caa Gln	gtg Val	3377
Phe	gcc Ala 1015	aag Lys	aac Asn	ttc Phe	Arg	gtg Val 1020	gcg Ala	gct Ala	gca Ala	Met	aag Lys 1025	acg Thr	tct Ser	gtg Val	ctg Leu	3425
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aag Lys	ctg Leu	Ile	gca Ala 1065	Asp	ctg Leu	cag Gln	ccc Pro	aac Asn 1070	Thr	gag Glu	tac Tyr	tcg Ser	Phe	Val	ctg Leu	3569
atg Met	Asn	cgt Arg 1080	Gly	ago Ser	agc Ser	Ala	999 Gly 1085	Gly	ctg Leu	cag Gln	cac His	ctg Leu 1090	Val	Ser	atc Ile	3617
cgc Arg	aca Thr 1095	Ala	Pro	gac Asp	cto Leu	ctg Leu 1100	Pro	cac His	aag Lys	ccg	ctg Leu 1105	Pro	gcc Ala	tct Ser	gcc Ala	3665
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ccc Pro	tcg Ser	ctt Leu	gto Val	agg Arg	Trp	tto Phe	tac Tyr	att Ile	gtt Val	Val	gta Val	ccc Pro	att Ile	gac Asp 1140	cgt Arg	3761
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PC1/0501/02	023
WO 01/55437  Val Gly Ser Met Leu Thr Pro Arg Trp Ser Thr Pro Glu Glu Leu  1150  1155	
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cgg cgg cgg cgg cag gca gaa cgt ctg aag cca tat gtg gct gct Arg Arg Arg Arg Gln Ala Glu Arg Leu Lys Pro Tyr Val Ala Ala 1175 1180 1185	3905
caa ctg gat gtg ctc ccg gag acc ttt acc ttg ggg gac aag aag aac Gln Leu Asp Val Leu Pro Glu Thr Phe Thr Leu Gly Asp Lys Lys Asn 1205	3953
tac cgg ggc ttc tac aac cgg ccc ctg tct ccg gac ttg agc tac cag  Tyr Arg Gly Phe Tyr Asn Arg Pro Leu Ser Pro Asp Leu Ser Tyr Gln  1210 1215 1220	4001
tgc ttt gtg ctt gcc tcc ttg aag gaa ccc atg gac cag aag cgc tat Cys Phe Val Leu Ala Ser Leu Lys Glu Pro Met Asp Gln Lys Arg Tyr 1235 1230 1235	4049
gcc tcc agc ccc tac tcg gat gag atc gtg gtc cag gtg aca cca gcc Ala Ser Ser Pro Tyr Ser Asp Glu Ile Val Val Gln Val Thr Pro Ala 1240 1245 1250	4097
cag cag cag gag gag ccg gag atg ctg tgg gtg acg ggt ccc gtg ctg Gln Gln Glu Glu Pro Glu Met Leu Trp Val Thr Gly Pro Val Leu	4145
gca gtc atc ctc atc ctc att gtc atc gcc atc ctc ttg ttc aaa Ala Val Ile Leu Ile Ile Leu Ile Val Ile Ala Ile Leu Leu Phe Lys 1270 1275 1280 1285	4193
agg aaa agg acc cac tct ccg tcc tct aag gat gag cag tcg atc gga Arg Lys Arg Thr His Ser Pro Ser Ser Lys Asp Glu Gln Ser Ile Gly 1290 1295 1300	4241
ctg aag gac tcc ttg ctg gcc cac tcc tct gac cct gtg gag atg cgg Leu Lys Asp Ser Leu Leu Ala His Ser Ser Asp Pro Val Glu Met Arg 1305 1310 1315	4289
agg ctc aac tac cag acc cca ggt atg cga gac cac cca ccc atc ccc Arg Leu Asn Tyr Gln Thr Pro Gly Met Arg Asp His Pro Pro Ile Pro 1320 1325 1330	4337
atc acc gac ctg gcg gac aac atc gag cgc ctc aaa gcc aac gat ggc  Ile Thr Asp Leu Ala Asp Asn Ile Glu Arg Leu Lys Ala Asn Asp Gly  1335 1340 1345	4385
ctc aag ttc tcc cag gag tat gag tcc atc gac cct gga cag cag ttc Leu Lys Phe Ser Gln Glu Tyr Glu Ser Ile Asp Pro Gly Gln Gln Phe 1350 1365	4433
acg tgg gag aat tca aac ctg gag gtg aac aag ccc aag aac cgc tat Thr Trp Glu Asn Ser Asn Leu Glu Val Asn Lys Pro Lys Asn Arg Tyr 1370 1375 1380	4481
gcg aat gtc atc gcc tac gac cac tct cga gtc atc ctt acc tct atc Ala Asn Val Ile Ala Tyr Asp His Ser Arg Val Ile Leu Thr Ser Ile 1385 1390 1395	4529
gat ggc gtc ccc ggg agt gac tac atc aat gcc aac tac atc gat ggc	4577

PCT/US01/02623 WO 01/55437 Asp Gly Val Pro Gly Ser Asp Tyr Ile Asn Ala Asn Tyr Ile Asp Gly 1405 tac ege aag cag aat gee tac ate gee aeg cag gge eee etg eee gag 4625 Tyr Arg Lys Gln Asn Ala Tyr Ile Ala Thr Gln Gly Pro Leu Pro Glu 1420 acc atg ggc gat ttc tgg aga atg gtg tgg gaa cag cgc acg gcc act 4673 Thr Met Gly Asp Phe Trp Arg Met Val Trp Glu Gln Arg Thr Ala Thr 1440 1435 1430 gtg gtc atg atg aca cgg ctg gag gag aag tcc cgg gta aaa tgt gat 4721 Val Val Met Met Thr Arg Leu Glu Glu Lys Ser Arg Val Lys Cys Asp 1450 cag tac tgg cca gcc cgt ggc acc gag acc tgt ggc ctt att cag gtg 4769 Gln Tyr Trp Pro Ala Arg Gly Thr Glu Thr Cys Gly Leu Ile Gln Val 1465 acc ctg ttg gac aca gtg gag ctg gcc aca tac act gtg cgc acc ttc 4817 Thr Leu Leu Asp Thr Val Glu Leu Ala Thr Tyr Thr Val Arg Thr Phe 1485 1480 gca ctc cac aag agt ggc tcc agt gag aag cgt gag ctg cgt cag ttt 4865 Ala Leu His Lys Ser Gly Ser Ser Glu Lys Arg Glu Leu Arg Gln Phe 1505 1500 1495 cag ttc atg gcc tgg cca gac cat gga gtt cct gag tac cca act ccc 4913 Gln Phe Met Ala Trp Pro Asp His Gly Val Pro Glu Tyr Pro Thr Pro 1520 1515 1510 ate etg gcc tte eta ega egg gtc aag gcc tgc aac eec eta gac gca 4961 Ile Leu Ala Phe Leu Arg Arg Val Lys Ala Cys Asn Pro Leu Asp Ala 1535 1530 ggg ccc atg gtg gtg cac tgc agc gcg ggc gtg ggc cgc acc ggc tgc 5009 Gly Pro Met Val Val His Cys Ser Ala Gly Val Gly Arg Thr Gly Cys 1550 1545 ttc atc gtg att gat gcc atg ttg gag cgg atg aag cac gag aag acg 5057 Phe Ile Val Ile Asp Ala Met Leu Glu Arg Met Lys His Glu Lys Thr 1565 1560 gtg gac atc tat ggc cac gtg acc tgc atg cga tca cag agg aac tac 5105 Val Asp Ile Tyr Gly His Val Thr Cys Met Arg Ser Gln Arg Asn Tyr 1585 1580 atg gtg cag acg gag gac cag tac gtg ttc atc cat gag gcg ctg ctg 5153 Met Val Gln Thr Glu Asp Gln Tyr Val Phe Ile His Glu Ala Leu Leu 1600 1595 gag gct gcc acg tgc ggc cac aca gag gtg cct gcc cgc aac ctg tat 5201 Glu Ala Ala Thr Cys Gly His Thr Glu Val Pro Ala Arg Asn Leu Tyr 1615 gcc cac atc cag aag ctg ggc caa gtg cct cca ggg gag agt gtg acc 5249 Ala His Ile Gln Lys Leu Gly Gln Val Pro Pro Gly Glu Ser Val Thr 1630 gec atg gag etc gag ttc aag ttg etg gec age tee aag gec eac aeg 5297 Ala Met Glu Leu Glu Phe Lys Leu Leu Ala Ser Ser Lys Ala His Thr 1640 tee ege tte ate age gee aac etg eec tge aac aag tte aag aac egg 5345

WO 01/55437	CT/US01/02623
Ser Arg Phe Ile Ser Ala Asn Leu Pro Cys Asn Lys Phe Lys Asn 1655 1660 1665	Arg
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Met Glu Thr Asp Pro Ala Ser Trp Pro Gln Pro Glu Pro Ala Gln	
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Leu Pro Gly Leu Tyr Ala Asp Phe Arg Ser Arg Thr Pro Arg Asp Ala	
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the second but are one transfer and transfer and are car	382
cct gcg ggc tgt ccc agg tgg ggc tgg aga tgc ctc agt gct gcc cag Pro Ala Gly Cys Pro Arg Trp Gly Trp Arg Cys Leu Ser Ala Ala Gln	302
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His Gly Arg Glu Pro Glu Ser Gly Ser Ala Ala Lys Val Ser Val Cys	
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Lys Gly Se	r Gln Thr A	la Pro Leu i	Asp Gly Ser	Pro Glu Asp	Gly Pro	
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924

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Cys Ser Arg Leu Phe Leu Ser Thr Lys Leu Lys Ala His Val Gln Ile 25 30 35	
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Val Leu Tyr Trp Val Phe Leu Trp Ser Arg Gly Asn Asn Phe Leu Thr 40 45 50 55	
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Met Val Ile Leu Asp Val Leu Glu Leu Tyr His Met Trp Phe 1 5 10	
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tgg tct ttc ctt tcc acc ata ttt ttg gat gtt gtg tgt tcc att tta Trp Ser Phe Leu Ser Thr Ile Phe Leu Asp Val Val Cys Ser Ile Leu 20 25 30	211
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45

cat cca His Pro	-		-				_	-			-		_		909
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ggcctc	atcc	cctga	ataco	a a	ccac	catgo	g gg	ttaai	teet	9999	gtcgg	gtg	aatta	agggaa	1433
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gcccgg	ggga	gtgg	gtgco	a g	accg	gggca	a gc	atct	cctc	ctad	ccag	gct a	agcc	gaaag	1553
ctggtg	aacc	gtgt	gcaco	c t	cccc	attgo	e te	cggta	aaag	ggad	cagat	gc	ccct	gccago	1613
cccagg	agag	cacci	tagto	g c	gcaca	acgga	gt	cccc	aggc	acad	cctct	ga i	agggg	ggaatt	1673
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                                                                     117
                                                     Met Lys Pro
                                                       1
tat tgt atg tat cct ttt ctg tct ggc ctc ctt agc tcc tta tta ttt
                                                                     165
Tyr Cys Met Tyr Pro Phe Leu Ser Gly Leu Leu Ser Ser Leu Leu Phe
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atg cta tgt gta ttg gat tac agg ata tat tgc atc aaa att tat gta Met Leu Cys Val Leu Asp Tyr Arg Ile Tyr Cys Ile Lys Ile Tyr Val 40 45 50	261
tcc att ata tta atg agc att tgg att att tca att taa gactatt Ser Ile Ile Leu Leu Met Ser Ile Trp Ile Ile Ser Ile * 55 60 65	310
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ctaagagagg aatttgtagg tcataggata tgtgtatgat cagcttgggt atacactacc	430
agttttctcc tgtcaaccag gcatgagaaa tctaattgcc ctatgtgctg actaaaacat	490
gaaattggga ggcctctaat tctaaccett ctggagaggg ccccccccc ccctggggg	550
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tagatttttt taaaaaatt	629

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Tyr Ser Tyr Met Val Phe Ser Val Asn Leu Tyr Lys \* 55 60 65

taatteteat tetgateett tetteattta aaactatgtt teteagttet getggtgttg 429
tgtttatatg gtgettttag eeactgeatt gtattetat tgetetgtet actgegtett 489
atttgeetgt teecetaagt gacagacace ttattegtte teeetgtace acaaacaatg 549
ettetgtgggt atagtggete acaettatag geteagatet teggggagga tgacgcagaa 609
agategettg ageecaggag teteaaacca aacegggeaa tgagacecaa aceteatete 669
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ggacgacgaa tgcagc atg tta atg tac cgc ggt gag gct ctt gaa gat Met Leu Met Tyr Arg Gly Glu Ala Leu Glu Asp
1 5 10

ttc aca ggc ccg gat tgt cgt ttt gtg aat ttt aaa aaa ggt gat cct 217
Phe Thr Gly Pro Asp Cys Arg Phe Val Asn Phe Lys Lys Gly Asp Pro

15 20 25

gta tat gtt tac tat aaa ctg gca aga gga tgg cct gaa gtt tgg gct 265 Val Tyr Val Tyr Lys Leu Ala Arg Gly Trp Pro Glu Val Trp Ala 30 35 40

gga agt gtt gga cgc act ttt gga tat ttt cca aaa gat tta atc cag 313 Gly Ser Val Gly Arg Thr Phe Gly Tyr Phe Pro Lys Asp Leu Ile Gln 45 50 55

gta gtt cat gaa tat acc aaa gaa gag cta caa gtt cca aca gat gag 361 Val Val His Glu Tyr Thr Lys Glu Glu Leu Gln Val Pro Thr Asp Glu 60 65 70

aat gta gaa gaa ctt tta ggg ttt ttg gaa ctg tac aat tct gca gct 457 Asn Val Glu Leu Leu Gly Phe Leu Glu Leu Tyr Asn Ser Ala Ala 95 100 105

aca gat tct gag aaa gct gta gaa caa act tta cag gat atg gaa aaa 505 Thr Asp Ser Glu Lys Ala Val Glu Gln Thr Leu Gln Asp Met Glu Lys

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, 110	115	120	
aac cct gaa tta tct aat ga Asn Pro Glu Leu Ser Asn Gl 125 13	u Arg Glu Pro Glu P	ect gaa cca gta gaa Pro Glu Pro Val Glu 35	553
gcc aac tca gag gaa agt ga Ala Asn Ser Glu Glu Ser As 140 145	t agt gta ttc tca g p Ser Val Phe Ser G 150	aa aac act gag gat lu Asn Thr Glu Asp 155	601
ctt cag gaa cag ttt aca ac Leu Gln Glu Gln Phe Thr Th 160	t tca aag cac cac t r Ser Lys His His S 165	cc cat ggc aac agg er His Gly Asn Arg 170	649
caa gca aat tat gct tca gg Gln Ala Asn Tyr Ala Ser Gl 175			697
gaa atg ctg caa gaa taa aa Glu Met Leu Gln Glu * 190	taaa agtgcccgaa agt	ggaaacc accaacccgg	751
cataagtott aggtotocaa agga	ccggaa aagaatgatg g	ctattaact tttgaaaaaa	811
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cgg ggt gga gga gtt aat tt Arg Gly Gly Gly Val Asn Pho 20	e Gly Glu Lys Asp A	ca aaa gtc ccc ggg la Lys Val Pro Gly 30	212
acc tgg aga gat gga gtc agg Thr Trp Arg Asp Gly Val Arg 35	g gtc cct gga gaa g g Val Pro Gly Glu G 45	ga gcc tct tgg gac ly Ala Ser Trp Asp 50	260
tca gac agg gcc agt cct gag Ser Asp Arg Ala Ser Pro Gli 55	g cga agg tac gga a 1 Arg Arg Tyr Gly I 60	ta ggt gag tga acc le Gly Glu * 65	308

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Leu His Tyr Tyr Met Tyr Val Phe Val Ser Arg Phe Ser Ile Tyr Tyr

tta aag tta ctt aga att ttt aag ttt tcc taa tataaaca agcatttgaa

50

Leu Lys Leu Leu Arg Ile Phe Lys Phe Ser \*

484

65 70

agaaactact ttaattgtta tgatgactaa acttgtctca aaccaaaaat atgcgctaaa 544 cactacgtag taagaatgag accagcctgg gcaacatagc aagacccttt ctctacaaaa 604 aaaagtttaa aaattatctg ggcgtggtgg cacacacctg tggtcctagc tactgggagg 664 cggaaggatt gcttgagccc aggagtttga ggctgcattg ggctgtgatc acacaccgtg 724 gcactccaag ctgggcgata gaaggaagat cgctctctac aaataaatac ataaatacaa 784 tttgaaaaga aacgggagtt gggaaccttg tcaagagggg caactactag agaagccatt tttaactatt attccatacg tgaacaaccc aggccgagat gtccctcccg ctggcaacat 904 gggatgcaaa cac 917 <210> 28

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gea gtt ttc cag agg ttc atg ttt cca ttt ctc ctt cct tgg ctt tcc 344 Ala Val Phe Gln Arg Phe Met Phe Pro Phe Leu Leu Pro Trp Leu Ser 5 10 15

tgc att ttt agc tcc agt caa aat tct att tat tat gta tca act ttt 392 Cys Ile Phe Ser Ser Ser Gln Asn Ser Ile Tyr Tyr Val Ser Thr Phe

ata aaa tgc ttg gct ttg aaa agt ata att aaa aga caa aga tct gaa 440 Ile Lys Cys Leu Ala Leu Lys Ser Ile Ile Lys Arg Gln Arg Ser Glu 40

att aat agg ggg ttt tta gct atc tat cat gca tta aga aat caa gtg 488 Ile Asn Arg Gly Phe Leu Ala Ile Tyr His Ala Leu Arg Asn Gln Val

acc agg tgt ggt ggc ctg taa tc ctagcacttt gggaggctga agtgggagga 541 Thr Arg Cys Gly Gly Leu

ccacttgage teaggagtte aagaceagee tgggeaacat ageaagacee tgtetetact

aaaaataaaa aaaattgacc agggggggg tgcatgcctg tagttccagc tacttgggac 661

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aat gcc aag aag agt tgc cag aag tac tta tca tct ttg aaa tta tcc Asn Ala Lys Lys Ser Cys Gln Lys Tyr Leu Ser Ser Leu Lys Leu Ser 15 20 25	158
act ttg tta tcc cct ttg ctg ttt ttg cct ttt tat acc cca tct ctt Thr Leu Leu Ser Pro Leu Leu Phe Leu Pro Phe Tyr Thr Pro Ser Leu 30 35 40	206
aaa gga tgg ggc att ttt gtt ttg agt ttt tat ttt atg tta att ata Lys Gly Trp Gly Ile Phe Val Leu Ser Phe Tyr Phe Met Leu Ile Ile 45 50 55 60	254
gcc gac tgt aac ctg ttc aaa ata att tag gagctctt ctagagttgg Ala Asp Cys Asn Leu Phe Lys Ile Ile Ile * 65 70	305
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			gly ggg			_				_			_	_		464
			ctt Leu													512
ttt Phe	ctt Leu	tat Tyr	tta Leu	aac Asn 40	att Ile	atg Met	ttt Phe	gtt Val	gta Val 45	gcc Ala	ttg Leu	tta Leu	aag Lys	gct Ala 50	att Ile	560
tta Leu	taa *	ttt	ttact	ag a	aata	attti	tg a	catt	tatt	a aa	attt	ttt	cta	tctc	caa	616
teta	attga	aga 1	taggo	cacat	t co	cttt	tgtel	ca(	ctcca	atta	taaa	aggg;	ag			665
		LO> :														
		L1> 1 L2> 1		•												
			Homo	sapi	iens											
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	<22	21> (														
	<22	22>	(61)	(66	59)											
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atg	gag	cgg	ggc	gca	gga	gcc	aag	ctg	ctg	ccg	ctg	ctg	ctg	ctt	ctg	108
мес 1	GIU	Arg	Gly	AIA 5	GIY	Ala	Lys	Leu	Leu 10	Pro	Leu	Leu	Leu	Leu 15	Leu	
000	~~~	205	~~+													
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tgg	cct	gag	atg	tgt	CCC	qat	qqa	ttc	ttc	acc	agc	aaa	ttc	t.ca	ctc	252
Trp	Pro 50	Glu	Met	Cys	Pro	Asp 55	ĞÎy	Phe	Phe	Ala	Ser 60	Gly	Phe	Ser	Leu	232
aag	gtt	gag	cct	ccc	caa	ggc	att	cct	ggc	gac	gac	act	gca	ctg	aat	300
65	val	GIU	Pro	PEO	70	GТĀ	тте	Pro	GТĀ	Asp 75	Asp	Thr	Ala	Leu	Asn 80	
aaa	atc	agg	ctg	cac	tgc	gcg	cgc	<b>a</b> aa	aac	gtc	cta	ggc	aat	acg	cac	348
$\sim$ 7							_	~ 7	_		Leu	~ 7	_		•	

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	85	90	95

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					tct Ser											396
					gcc Ala											444
					ggt Gly											492
					gag Glu 150											540
					agt Ser											588
					gga Gly											636
					ttc Phe					tga *	acgg	gege	c gt	egee	geeg	687
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age ctt get aag ace ace cag eee ate tee atg gae tea tat gaa gga 96 Ser Leu Ala Lys Thr Thr Gln Pro Ile Ser Met Asp Ser Tyr Glu Gly 20 25 30

caa gaa gtg aac ata acc tgt agc cac aac aat gct aca aat gat 144 Gln Glu Val Asn Ile Thr Cys Ser His Asn Asn Ile Ala Thr Asn Asp 35 40 45

tat atc acg tgg tac caa cag ttt ccc agc caa gga cca cga ttt att

Tyr Ile Thr Trp Tyr Gln Gln Phe Pro Ser Gln Gly Pro Arg Phe Ile

50 . 55 60

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WO 01/55437 PCT/US01/02623 Ile Gln Gly Tyr Lys Thr Lys Val Thr Asn Glu Val Ala Ser Leu Phe atc cct gcc gac aga aag tcc agc act ctg agc ctg ccc cgg gtt tcc 288 Ile Pro Ala Asp Arg Lys Ser Ser Thr Leu Ser Leu Pro Arg Val Ser ctg agc gac act gct gtg tac tac tgc ctc gtg ggt gac aca cag tga 336 Leu Ser Asp Thr Ala Val Tyr Tyr Cys Leu Val Gly Asp Thr.Gln \* gacagatggg cotgcacctg tgccgttttc ctctgtgggg tgggagtcac agcctagaaa 396 gaagtccaaa agtgctttct aaaattttta ttttcaaaag gtattagcaa atttatgtat 456 tettetacta tttgcaaaat caatettatt tatttttaa ataggtattt caettatgtg atctaaaatt aaaaagtat aaaagggaa 545 <210> 33 <211> 493 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (31) .. (414) <400> 33 attgagggct gtgttataac tatctattcg atg atg aag ata ccc cac caa 51 Met Met Lys Ile Pro His Gln acc caa aaa aag aga tet ete gag gat eeg aat teg egg eeg egt ega 99 Thr Gln Lys Lys Arg Ser Leu Glu Asp Pro Asn Ser Arg Pro Arg Arg 10 ccg cgc ggg gaa ggg gag acg tgg ggt aga gtg acc atg acg aaa tta 147 Pro Arg Gly Glu Gly Glu Thr Trp Gly Arg Val Thr Met Thr Lys Leu gcg cag tgg ctt tgg gga cta gcg atc ctg ggc tcc acc tgg gtg gcc 195 Ala Gln Trp Leu Trp Gly Leu Ala Ile Leu Gly Ser Thr Trp Val Ala ctg acc acg gga gcc ttg ggc ctg gag ctg ccc ttg tcc tgc cag gaa 243 Leu Thr Thr Gly Ala Leu Gly Leu Glu Leu Pro Leu Ser Cys Gln Glu 60 gtc ctg tgg cca ctg ccc gcc tac ttg ctg gtg tcc gcc ggc tgc tat 291 Val Leu Trp Pro Leu Pro Ala Tyr Leu Leu Val Ser Ala Gly Cys Tyr gcc ctg ggc act gtg ggc tat cgt gtg gcc act ttt cat gac tgc gag 339 Ala Leu Gly Thr Val Gly Tyr Arg Val Ala Thr Phe His Asp Cys Glu 90 gac gcc gca cgc gag ctg cag agc cag ata cag gag gcc cga gcc gac 387 Asp Ala Ala Arg Glu Leu Gln Ser Gln Ile Gln Glu Ala Arg Ala Asp 105 115.

tta gcc cgc agg ggg ctg cgc ttc tga cagcc taaccccatt cctgtgcgga Leu Ala Arg Arg Gly Leu Arg Phe 125 cagecettee teccatttee cattaaagag ecagtttatt ttetaaaaaa aaaa 493 <210> 34 <211> 1900 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (314)..(709) <220> <221> misc\_feature <222> (1) ... (1900) <223> n = a,t,c or g<400> 34 60 atttggccct cgaggccaag aattcggcac gagcataagg ttgtagtagc aggagccctc tatettttgt tegggnneat ggaaggggte eteanagenn nngagaetea gaetgatett gettacttgg cetttatece ettggettte etagaceetg gettgegeag etggatgeag 180 acaacatccc cccaccaccc aagagggagg gtagctcttc cgccaccagg ggcaagcaca tttgtatcgg catttcacca acacgettat tttggcagtg gcagcatcca ttgtgtttat 300 349 atg aag ttc aga ata gtg aca tgt cag tcg gac tgg catctggaca acc Met Lys Phe Arg Ile Val Thr Cys Gln Ser Asp Trp 5 cgg gag ctg tgg gta gac gat gcc atc tgg cgc ttg ctg ttc tcc atg 397 Arg Glu Leu Trp Val Asp Asp Ala Ile Trp Arg Leu Leu Phe Ser Met 20 15 atc ctc ttt gtc atc atg gtt ctc tgg cga cca tct gca aac aac cag 445 Ile Leu Phe Val Ile Met Val Leu Trp Arg Pro Ser Ala Asn Asn Gln 30 agg ttt gcc ttt tca cca ttg tct gag gaa gag gag gat gaa caa 493 Arg Phe Ala Phe Ser Pro Leu Ser Glu Glu Glu Glu Glu Asp Glu Gln 50 45 aag gag cct atg ctg aaa gaa agc ttt gaa gga atg aaa atg aga agt 541 Lys Glu Pro Met Leu Lys Glu Ser Phe Glu Gly Met Lys Met Arg Ser 65 acc aaa caa gaa ccc aat gga aat agt aaa gtt aac aaa gca cag gaa 589 Thr Lys Gln Glu Pro Asn Gly Asn Ser Lys Val Asn Lys Ala Gln Glu 80 85 gat gat ttg aag tgg gta gaa gag aat gtt cct tct tct gtg aca gat 637 Asp Asp Leu Lys Trp Val Glu Glu Asn Val Pro Ser Ser Val Thr Asp 100

685

gta gca ctt cca gcc ctt ctg gat tca gat gag gaa cga atg atc aca

Val Ala Leu Pro Ala Leu Leu Asp Ser Asp Glu Glu Arg Met Ile Thr

110	115	120

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<220>

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ttggetetgg tgetggtgge cgetetgtgg ggtggcacge agecgetget gaagcgggec 180

tccg	gccgg	gec 1	tgcag	geggg	gt to	atga	agccg	gaco	tggg	gccc	agca	gtt	gct a	acago	gag	237
_	_				_					_	_			ctc		285
Met 1	гàг	inr	Leu	5	Leu	ASII	inr	GIU	10	Leu	Mec.	PIO	PHE	Leu 15	Leu	
														aca		333
Asn	Gln	Gly	Gly 20	Ser	Leu	Leu	Tyr	Tyr 25	Leu	Thr	Leu	Ala	Ser 30	Thr	Asp	
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Leu	Thr	Leu 35	Ala	Val	Pro	Ile	Cys 40	Asn	Ser	Leu	Ala	Ile 45	Ile	Phe	Thr	
														cga		429
Leu	Ile 50	Val	Gly	Lys	Ala	Leu 55	Gly	Glu	Asp	Ile	Gly 60	Gly	Lys	Arg	Ala	
														atc		477
Val 65	Ala	Gly	Met	Val	Leu 70	Thr	Val	Ile	Gly	Ile 75	Ser	Leu	Cys	Ile	Thr 80	
_		_				_	-		_	_			_	ggc		525
Ser	Ser	Val	Pro	Trp 85	Thr	Ala	Glu	Leu	Gln 90	Leu	His	Gly	Lys	Gly 95	Gln	
														act		573
Leu	Gln	Thr	Leu 100	Ser	Gln	Lys	Cys	Lys 105	Arg	Glu	Ala	Ser	Gly 110	Thr	Gin	
		Arg	Phe			atga	agg (	ggtg	gaac	cg ag	gggaa	agaaq	g gta	agaga	agct	627
		115														
gtg	agcc	cca i	gccc	cacci	tg a	ctcc	agca	c ac	ctgg	cgag	tagi	agc	tgt (	caata	aaatct	687
atg	gtaa	aca	gacaa	agag	ga g	gtgg	aagg	c ca	taca	gaat	ggag	gccgt	tga 🤉	gtate	gccag	747
cct	ccag	ctc	tcago	ccag	ga g	gtcc	ccaa	c cc	caag	gaag	gaag	gaaa	ctg	gaaat	tagga	807
act	gctt	cct	catti	taaca	aa g	gtgc	ttcti	t tt	catg	tgat	gag	gccci	tgt (	gaaga	aaggga	867
															gtctga	927
_		=						•							gtcaaa	987
															gtgtgg	1047
ggag	gctt	gct	tcttq	ggct	ga at	tggt	ctgc	t ggg	ggtc	tggc	atag	gaaag	gca 🤉	gatgg	gctt	1105

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caaccccaga ggccggactc ctggattcat ct	ccctagct tccctgggcc tgccttagcc 180
gccagtcgca gccgaggcga agagagcgaa gg	agggaagt gggggggct agctggggct 240
agaaggccag gagagggcgg ggtgggcggc cg	tttggggt gggggtcagg gtgactcact 300
cgtctgcatt cagggcaggt gttggctctg gt	gctggtgg ccgctctgtg gggtggcacg 360
cagcegetge tgaageggge eteegeegge et	gcagcggg ttcatgagcc gacctgggcc 420
cagcagttgc tacaggag atg aag acc ct Met Lys Thr Le 1	c ttc ttg aat act gag tac ctg 47] u Phe Leu Asn Thr Glu Tyr Leu 5 10
atg ccc ttt ctc ctc aac cag tgt gga Met Pro Phe Leu Leu Asn Gln Cys Gly 15 20	Ser Leu Leu Tyr Tyr Leu Thr
ttg gca tcg aca gat ctg acc ctg gct Leu Ala Ser Thr Asp Leu Thr Leu Ala 30 35	gtg ccc atc tgt aac tct ctg 567 Val Pro Ile Cys Asn Ser Leu 40
gct atc atc ttc aca ctg att gtt ggg Ala Ile Ile Phe Thr Leu Ile Val Gly 45 50	aag gcc ctt gga gaa gat att 615 Lys Ala Leu Gly Glu Asp Ile 55
ggt gga aaa cga gca gtt gct ggc atg Gly Gly Lys Arg Ala Val Ala Gly Met 60 65	gtg ctc acc gtg ata gga att 663 Val Leu Thr Val Ile Gly Ile 70 75
tca ctc tgc atc aca agc tca gtg agt Ser Leu Cys Ile Thr Ser Ser Val Ser 80	aag acc cag ggg caa cag tct 711 Lys Thr Gln Gly Gln Gln Ser 85 90
acc ctt tga gtgggcc gaacccactt ccag Thr Leu *	ctctgc tgcctccagg aagcccctgg 767
gccatgaagt gctggcagtg agcggatgga cc	tagcactt eccetetetg geettagett 827
cotcetetet tatggggata acagetacet ca	tggatcac aataagagaa caagagtgaa 887
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170 175 180

			170					175					180			
		gcc Ala 185														808
		atc Ile														856
		aca Thr														904
		cct Pro				_	-	_			_		_			952
_	_	atc Ile	-					_	_	_				_	_	1000
		ctg Leu 265													ggc '	1048
		aag Lys														1096
		tcc Ser														1144
ggc Gly	aac Asn	aag Lys	cag Gln	cac His 315	aac Asn	agt Ser	ccc Pro	acc Thr	tgg Trp 320	gat Asp	gac Asp	ccc Pro	acg Thr	ctg Leu 325	gcc Ala	1192
		ctc Leu														1240
ccc Pro	gag Glu	gtc Val 345	tcc Ser	cag Gln	gtg Val	acc Thr	aag Lys 350	tcc Ser	agc Ser	cca Pro	gag Glu	caa Gln 355	agc Ser	tac Tyr	cag Gln	1288
GJA aaa	gac Asp 360	atg Met	tac Tyr	ccc	acc Thr	egg Arg 365	ggc Gly	gtg Val	ggc	tat Tyr	gag Glu 370	acc Thr	atc Ile	ctg Leu	aaa Lys	1336
gag Glu 375	cag Gln	aag Lys	ggt Gly	cag Gln	agc Ser 380	atg Met	ttc Phe	gtg Val	gag Glu	aac Asn 385	aag Lys	gcc Ala	ttt Phe	tcc Ser	atg Met 390	1384
gat Asp	gag Glu	ccg Pro	gtt Val	gca Ala 395	gct Ala	aag Lys	agg Arg	ccg Pro	gtg Val 400	tca Ser	cca Pro	tac Tyr	agc Ser	ggg Gly 405	tac Tyr	1432
aat Asn	gly aaa	cag Gln	ctg Leu 410	ctg Leu	acc Thr	agt Ser	gtg Val	tac Tyr 415	cag Gln	ccc Pro	act Thr	gag Glu	atg Met 420	gcc Ala	ctg Leu	1480
atg Met	cac His	aaa Lys	gtt Val	ccg Pro	tcc Ser	gaa Glu	gga Gly	gct Ala	tac Tyr	gac Asp	atc Ile	atc Ile	ctc Leu	cca Pro	cgg Arg	1528

430 435 425 1576 ged add ged aad agd dag gtg atg ggd agt ged aad teg add ctg Ggg Ala Thr Ala Asn Ser Gln Val Met Gly Ser Ala Asn Ser Thr Leu Arg 445 450 440 get gaa gae atg tae teg gee cag age cae cag geg gee aca eeg eeg 1624 Ala Glu Asp Met Tyr Ser Ala Gln Ser His Gln Ala Ala Thr Pro Pro 460 455 aaa gac ggc aag aac tot cag gto ttt aga aac coc tac gtg tgg gac 1672 Lys Asp Gly Lys Asn Ser Gln Val Phe Arg Asn Pro Tyr Val Trp Asp

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480

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tggagattee tgeaacetea agagaettee eaggegetea ggeetggate ttgeteetet 2032

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475

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10 15 20

acc cta tca ttg tta ttg aaa ttg tca cat tac tct tgt ctt tgg gtt

Thr Leu Ser Leu Leu Lys Leu Ser His Tyr Ser Cys Leu Trp Val

25

30

35

aaa aaa gac ttt aaa gac tcc tcg ttt tac aat agc aat aat agc 197 Lys Lys Asp Phe Lys Asp Ser Ser Phe Tyr Asn Ser Asn Asn Ser 40 45

aat agc aat cat tgt aaa tct tta ttg agc act cac tat atg cca ggc
Asn Ser Asn His Cys Lys Ser Leu Leu Ser Thr His Tyr Met Pro Gly
55 60 65

gct gta att agt aat tta tgc ctt atc tca tgt aaa gtt tcc agc agc 293
Ala Val Ile Ser Asn Leu Cys Leu Ile Ser Cys Lys Val Ser Ser Ser
70 75 80 85

cct att aag cag aca cat ggc att tcc atg tta cag atg aag aga ctg Pro Ile Lys Gln Thr His Gly Ile Ser Met Leu Gln Met Lys Arg Leu 90 95 100	341
aaa cac aca tta gct cgc ctt gcc cca ggg aca cat ggt ggg agc cag Lys His Thr Leu Ala Arg Leu Ala Pro Gly Thr His Gly Gly Ser Gln 105 110 115	389
aac tagg agttgageee aggeataetg atgeetggtg caettggaeg etgetgtaea Asn	446
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geggagetgt gtetgtteec aggagteett eggeggetgt tgtgteagtg geetgatege	180
g atg ggg aca aag gcg caa gtc gag agg aaa ctg ttg tgc ctc ttc Met Gly Thr Lys Ala Gln Val Glu Arg Lys Leu Leu Cys Leu Phe 1 5 10 15	226
ata ttg gcg atc ctg ttg tgc tcc ctg gca ttg ggc agt gtt aca gtg Ile Leu Ala Ile Leu Cys Ser Leu Ala Leu Gly Ser Val Thr Val 20 25 30	274
Cac tot tot gaa cot gaa gto aga att cot gag aat aat cot gtg aag His Ser Ser Glu Pro Glu Val Arg Ile Pro Glu Asn Asn Pro Val Lys 35 40 45	322
ttg tcc tgt gcc tac tcg ggc ttt tct tct ccc cgt gtg gag tgg aag Leu Ser Cys Ala Tyr Ser Gly Phe Ser Ser Pro Arg Val Glu Trp Lys 50 55 60	<b>370</b>
ttt gac caa gga gac acc acc aga ctc gtt tgc tat aat aac aag atc Phe Asp Gln Gly Asp Thr Thr Arg Leu Val Cys Tyr Asn Asn Lys Ile 65 70 75	418
aca gct tcc tat gag gac cgg gtg acc ttc ttg cca act ggt atc acc Thr Ala Ser Tyr Glu Asp Arg Val Thr Phe Leu Pro Thr Gly Ile Thr 80 85 90 95	466
ttc aag tcc gtg aca cgg gaa gac act ggg aca tac act tgt atg gtc Phe Lys Ser Val Thr Arg Glu Asp Thr Gly Thr Tyr Thr Cys Met Val 100 105 110	514
tct gag gaa ggc ggc aac agc tat ggg gag gtc aag gtc aag ctc atc Ser Glu Glu Gly Gly Asn Ser Tyr Gly Glu Val Lys Val Lys Leu Ile	562

115 120 125

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555			-	_	_	gat ggt tcc Asp Gly Ser	658
						atg cct acg Met Pro Thr 175	706
	_		-			gtc ctg aat Val Leu Asn 190	754
ccc aca aca Pro Thr Thr			_	_	Ser Ala	tct gat act Ser Asp Thr 205	802
gga gaa tad Gly Glu Tyr 210	Ser Cys	Glu Ala					850
						ggg gtc atc Gly Val Ile	898
gtg gca gcc Val Ala Ala 240							946
ggc atc tgg Gly Ile Trp							994
ggg act tcg Gly Thr Ser					Pro Ser I		1042
gaa gga gaa Glu Gly Glu 290		Gln Thr				cctggtcggc	1092
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69

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tgc tca gaa caa gat ggt tcc cca cct tct gaa tac acc tgg ttc aaa

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aac Asn 145	tct Ser	tcc Ser	tat Tyr	gtc Val	ctg Leu 150	aat Asn	ccc Pro	aca Thr	aca Thr	gga Gly 155	gag Glu	ctg Leu	gtc Val	ttt Phe	gat Asp 160	480
ccc Pro	ctg Leu	tca Ser	gcc Ala	tct Ser 165	gat Asp	act Thr	gga Gly	gaa Glu	tac Tyr 170	agc Ser	tgt Cys	gag Glu	gca Ala	cgg Arg 175	aat Asn	528
ggg Gly	tat Tyr	Gly 999	aca Thr 180	ccc Pro	atg Met	act Thr	tca Ser	aat Asn 185	gct Ala	gtg Val	cgc Arg	atg Met	gaa Glu 190	gct Ala	gtg Val	576
											ctt Leu					624
Leu	ctg Leu 210	gga Gly	atc Ile	ttg Leu	gtt Val	ttt Phe 215	ggc	atc Ile	tgg Trp	ttt Phe	gcc Ala 220	tat Tyr	agc Ser	cga Arg	ggc Gly	672
cac His 225	ttt Phe	gac Asp	aga Arg	aca Thr	aag Lys 230	aaa Lys	Gly ggg	act Thr	tcg Ser	agt Ser 235	aag Lys	aag Lys	gtg Val	att Ile	tac Tyr 240	720
agc Ser	cag Gln	cct Pro	agt Ser	gcc Ala 245	cga Arg	agt Ser	gaa Glu	gga Gly	gaa Glu 250	ttc Phe	aaa Lys	cag Gln	acc Thr	tcg Ser 255	tca Ser	768
ttc Phe																777
	<21 <21	.0> 4 .1> 1 .2> D .3> H	.683 NA	sapi	ens.											
		1> C		(1	333)							•				
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															aatca	120
															ctgcc	180
															cagec	240

PCT/US01/02623

WO 01/55437

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				egeegeeget ge		80
attccttgtg go			agcc atg	g atg atc cac E Met Ile His	ggc ttc 53	32
cag agc agc o	cac cgg gat His Arg Asp 10	Phe Cys Ph	tc ggg ccc he Gly Pro 15	tgg aag ctg a Trp Lys Leu 5	acg gcg 59 Thr Ala	80
tcc aag acc Ser Lys Thr	cac atc atg His Ile Met	aag tcg go Lys Ser A: 30	cg gat gtg la Asp Val	gag aaa tta g Glu Lys Leu 3 35	gcc gat 6 Ala Asp	28
gaa tta cat Glu Leu His 40	atg cca tct Met Pro Ser	ctc cct ga Leu Pro G 45	aa atg atg lu Met Met	ttt gga gac a Phe Gly Asp 2	aac gtt 6 Asn Val	76
tta aga atc Leu Arg Ile 55	cag cat ggg Gln His Gly 60	tct ggc t Ser Gly P	tt gga att he Gly Ile 65	gag ttc aat Glu Phe Asn	gct aca 7 Ala Thr 70	24
gat gcg tta Asp Ala Leu	aga tgt gta Arg Cys Val 75	aac aac t Asn Asn T	ac caa gga Tyr Gln Gly 80	atg ctt aaa Met Leu Lys	gtg gcc 7 Val Ala 85	172
tgt gct gaa Cys Ala Glu	gag tgg caa Glu Trp Gln 90	Glu Ser A	agg acg gag Arg Thr Glu 95	ggt gaa cac Gly Glu His 100	tcc aaa 8 Ser Lys	320
gag gtt att Glu Val Ile 105	aaa cca tat Lys Pro Tyr	gat tgg a Asp Trp T	acc tat aca Thr Tyr Thr	aca gat tat Thr Asp Tyr 115		368
acc tta ctt Thr Leu Leu 120	gga gaa tct Gly Glu Ser	ctt aag t Leu Lys I 125	tta aag gtt Leu Lys Val	gta cct aca Val Pro Thr 130		916
cat ata gat His Ile Asp 135	aca gaa aaa Thr Glu Lys 140	Leu Lys A	gcc aga gaa Ala Arg Glu 145	a cag att aag 1 Gln Ile Lys 5	ttt ttt S Phe Phe 150	964
gaa gaa gtt Glu Glu Val	ctc ctt ttt Leu Leu Phe 155	gag gat g Glu Asp (	gaa ctt cat Glu Leu His 160	t gat cat gga s Asp His Gly	gtt tca 10 Val Ser 165	012
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ttg cgg ttt Leu Arg Phe 185	ttc ttg aga Phe Leu Arg	att gat o Ile Asp (	ggg gtg ctt Gly Val Let	t atc aga atg u Ile Arg Met 195	J	108
acg aga ctt Thr Arg Leu 200	tac cat gag Tyr His Glu	get gae a Ala Asp 1 205	aag acc tad Lys Thr Ty	c atg tta cga r Met Leu Arg 210	gaa tat 1 Glu Tyr	156
acg tca cga Thr Ser Arg 215	gaa agc aaa Glu Ser Lys 220	Ile Ser	agt ttg atg Ser Leu Mer 22	g cat gtt cca t His Val Pro 5	cct tcc 1 Pro Ser 230	.204

Ctc ttc acg gaa cct aat gaa ata tcc cag tat tta cca ata aag gaa Leu Phe Thr Glu Pro Asn Glu Ile Ser Gln Tyr Leu Pro Ile Lys Glu 235 240 245	1252
gca gtt tgt gag aag cta ata ttt cca gaa aga att gat cct aac cca Ala Val Cys Glu Lys Leu Ile Phe Pro Glu Arg Ile Asp Pro Asn Pro 250 255 260	1300
gca gac tca caa aaa agt aca caa gtg gaa taa aatgtgat acaacatata Ala Asp Ser Gln Lys Ser Thr Gln Val Glu * 265 270	1351
ctcactatgg aatctgactg gacaccttgg ctatttgtaa ggggttattt ttattatgag	1411
aattaattgc cttgtttatg tacagatttt ctgtagcctt aaaggaaaaa aaaataaaga	1471
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cagatttata ttttctggag ttaaatttgg atgatttcta aattatcaca aagtgggacc	1591
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	gag Glu															596
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	tgc Cys 100															692
	Gly aaa															740
	atg Met															788
	tgc Cys						_						_	_		836
	gaa Glu															884
	atg Met 180				-	-	-		-		_		_			932
	tcc Ser															980
	gtt Val				Leu								_		_	1028
	ggt Gly			Tyr							aaaa	agag	c tt	tgtt	tggt	1079
ccc	agag	gta	atat	ctct	tc t	aatt	tttt	c tc	acct	tgat	aca	agta	aag	aact	ttcgat	1139
ata	tggt	ctg	acac	agct	aa t	atga	tgtt	a cc	tttt	ttgt	caa	agtt	ctc	tttt	acagag	1199
gtg	tagg	acg	ataa	gcat	tt g	tacc	taaa	g ct	ttca	aaca	tgc	cctc	tgg	gatt	atgtcg	1259
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agc	ttct	ctc	tgca	gage	at g	acgg	tgtc	c ag	gctc	tcta	ggc	agag	ctc	gcta	attgaa	1379
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<220>

<221> CDS

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<400> 43

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								ggt Gly 90								823
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								ggt Gly								967
								gta Val								1015
								act Thr 170								1063
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		Cys	_			_		aca Thr		_						1159
		_		-		Gly		aga Arg		_	Ala				taa	1207
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tta	tcct	gct	ccac	catg	cc a	tcaa	.agaa	g aa	tatc	aact	tga	tccc	agc	tgcc	gtaaa	a 1867
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gattctggag tataccaata	tetgagacaa	cacatggcat	caaccacaat	ggtaggggta	1987
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Asp Val Asn Tyr Trp Thr Ser Arg Tyr Trp Leu Asn Gly Asp Phe Arg

aaa gga gat gtg tcc ctg acc ata ggg aat gtg act cta gca gac agt

Lys Gly Asp Val Ser Leu Thr Ile Gly Asn Val Thr Leu Ala Asp Ser

ggg atc tac tgc tgc cgg atc caa atc cca ggc ata atg aat gaa

Gly Ile Tyr Cys Cys Arg Ile Gln Ile Pro Gly Ile Met Asn Asp Glu

60

120

170

218

266

314

362

410

458

506

115

125 130 135

125 130 135	
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acc agg gga cat ggc cca gca gag aca cag aca ctg ggg agc ctc cct Thr Arg Gly His Gly Pro Ala Glu Thr Gln Thr Leu Gly Ser Leu Pro 155 160 165	650
gat ata aat cta aca caa ata tcc aca ttg gcc aat gag tta cgg gac Asp Ile Asn Leu Thr Gln Ile Ser Thr Leu Ala Asn Glu Leu Arg Asp 170 175 180 185	698
tct aga ttg gcc aat gac tta cgg gac tct gga gca acc atc aga ata Ser Arg Leu Ala Asn Asp Leu Arg Asp Ser Gly Ala Thr Ile Arg Ile 190 195 200	746
ggc atc tac atc gga gca ggg atc tgt gct ggg ctg gct ctg gct ctt Gly Ile Tyr Ile Gly Ala Gly Ile Cys Ala Gly Leu Ala Leu Ala Leu 205 210 215	794
atc ttc ggc gct tta att ttc aaa tgg tat tct cat agc aaa gag aag Ile Phe Gly Ala Leu Ile Phe Lys Trp Tyr Ser His Ser Lys Glu Lys 220 225 230	842
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acc att gaa gag aac gta tat gaa gtg gag gag ccc aat gag tat tat Thr Ile Glu Glu Asn Val Tyr Glu Val Glu Glu Pro Asn Glu Tyr Tyr 270 275 280	986
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gagtettget etgttgeeca ggetggagtg caatggeaca atettggete aetgeaaget	1569
cegeeteetg ggttegageg attettetge etcageetee tgagtggetg ggattacagg	1629

WO 01/55437				PCT/US01/0	2623
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ttggccagtg tggtctcaaa ctcctgacct catgatttgc ctgcctcggc ctcccaaagc

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atgeeteact geageetega cetecetggg eteaageaat eeteeeactt cageeteeag 300

360

agtggctggg accacagtgt ggctgtccag ctgggctgag tcgcccaaga aggacgtgac aggtgccgac gccaccgccg agccc atg atc ctg gaa cag tac gtg gtg gtg 412 Met Ile Leu Glu Gln Tyr Val Val Val

460 tcc aac tat aag aag cag gag aac tcg gag ctg agc ctc cag gcc ggg Ser Asn Tyr Lys Lys Gln Glu Asn Ser Glu Leu Ser Leu Gln Ala Gly 15

508 gag gtg gtg gat gtc atc gag aag aac gag agc ggc tgg tgg ttc gtg Glu Val Val Asp Val Ile Glu Lys Asn Glu Ser Gly Trp Trp Phe Val 35 30

age act tet gag gag cag gge tgg gte eet gee ace tae etg gag gee 556 Ser Thr Ser Glu Glu Gln Gly Trp Val Pro Ala Thr Tyr Leu Glu Ala 50

cag aat ggt act cgg gat gac tcc gac atc aac acc tct aag act gga 604 Gln Asn Gly Thr Arg Asp Asp Ser Asp Ile Asn Thr Ser Lys Thr Gly 60

652 gaa gtg tcc aag aga cgc aag gcc cat ctg cgg cgc ctg gat cgc cgg Glu Val Ser Lys Arg Arg Lys Ala His Leu Arg Arg Leu Asp Arg Arg 75

700 tgg acc ctg ggc ggg atg gtc aac agg cag cac agc cga gag gag aag Trp Thr Leu Gly Gly Met Val Asn Arg Gln His Ser Arg Glu Glu Lys 105 95 90

748 tat gtc acc gtg cag cct tac acc agc caa agc aag gac gag att ggc Tyr Val Thr Val Gln Pro Tyr Thr Ser Gln Ser Lys Asp Glu Ile Gly 115 110

796 ttt gag aag ggc gtc aca gtg gag gtg atc cgg aag aat ctg gaa ggc

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														aac Asn		892
														aac Asn		940
_		_	_				_	_	_				_	gaa Glu 200	~ ~	988
				-			_	_	_			_	_	ccc Pro		1036
														agg Arg		1084
														gcc Ala		1132
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cct Pro	tct Ser	gtt Val	gag Glu 285	gtg Val	gag Glu	tac Tyr	tac Tyr	acc Thr 290	att Ile	gcc Ala	gaa Glu	ttc Phe	cag Gln 295	tcg Ser	tgc Cys	1276
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ccc Pro 410	gtg Val	gag Glu	gac Asp	aga Arg	gcc Ala 415	tca Ser	Gly ggg	gag Glu	agg Arg	cgg Arg 420	cct Pro	gcc Ala	cag Gln	ccc Pro	cac His 425	1660
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													aac Asn			1948
	-												tgc Cys 535	_		1996
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_		_		_	_	_	_			•			ccc Pro	_	_	2092
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	-	_		_	_			-					cga Arg	_		2188
													cgc Arg 615			2236
_				_		_				_			aag Lys	_		2284
gat	tcg	gag	ctg	ccc	ccg	cag	acg	gcc	tcc	gag	gct	ccc	agt	gag	<b>a</b> aa	2332

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gag Glu	aag Lys	atc Ile	gag Glu 765	agg Arg	cgc Arg	gtc Val	caa Gln	gca Ala 770	ctg Leu	aac Asn	acc Thr	gtc Val	aac Asn 775	cag Gln	agc Ser	2716
Lys	Lys	Ala 780	Thr	Pro	Pro	atc Ile	Pro 785	Ser	Lys	Pro	Pro	Gly 790	Gly	Phe	Gly	2764
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Asp	Gly	Leu	Arg 845	Gly	Val	cga Arg	Arg	Asn 850	Ser	Ser	Phe	Ser	Thr 855	Ala	Arg	2956
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3196 gag gag aca gca ggc ttc cag gag ggg gtg tcc atg gag gtt ctg gag Glu Glu Thr Ala Gly Phe Gln Glu Gly Val Ser Met Glu Val Leu Glu 930

agg aac cct aat ggc tgg tgg tac tgc cag atc ctg gat ggt gtg aag 3244 Arg Asn Pro Asn Gly Trp Trp Tyr Cys Gln Ile Leu Asp Gly Val Lys

ccc ttc aaa ggc tgg gtg cct tcc aac tac ctt gag aaa aag aac tag 3292 Pro Phe Lys Gly Trp Val Pro Ser Asn Tyr Leu Glu Lys Lys Asn 960 955

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acttgtaatg ccccaaggct tgatttttc cagataatgg ctctatcgtt gcacataccc 180

tgattctgtc agt atg tgt cat tgg caa aat agc ttt ctc tgc caa agc 229

Met Cys His Trp Gln Asn Ser Phe Leu Cys Gln Ser 1 5 10

ttt ctg acc ttt ggc tcc atc tta gct ttg tta gca gga aag gcc tgc 277
Phe Leu Thr Phe Gly Ser Ile Leu Ala Leu Leu Ala Gly Lys Ala Cys
25

tac cca gag tca gag tca atc aga gaa ttg ttc atg tgg tcc tta gaa 325 Tyr Pro Glu Ser Glu Ser Ile Arg Glu Leu Phe Met Trp Ser Leu Glu 30 35 40

PCT/US01/02623 WO 01/55437 ctt tac tcc tta ccc ttt tat ctt ttc ttt aaa ctt tcg cct cta aat Leu Tyr Ser Leu Pro Phe Tyr Leu Phe Phe Lys Leu Ser Pro Leu Asn 55 45 ctg cca ggg aaa ttg gga ctt ata gaa acc ttg tca act tgt ttg ggt 421 Leu Pro Gly Lys Leu Gly Leu Ile Glu Thr Leu Ser Thr Cys Leu Gly 70 65 caa aaa tta gat cct gtg tta gaa act ctg caa aga gtg aga tcc atg 469 Gln Lys Leu Asp Pro Val Leu Glu Thr Leu Gln Arg Val Arg Ser Met 85 80 gca tca ttg atc gcc aac ttc ttt gtt cct ttc atc cag aag aaa ggt 517 Ala Ser Leu Ile Ala Asn Phe Phe Val Pro Phe Ile Gln Lys Lys Gly 105 100 cag ctc att acg taa gaaacttttc atcaggaaaa gcagacaacc gataaaaaac 572 Gln Leu Ile Thr \* 110 632 agaaactaag tattctgcaa ggaaacctgg tttaaggaga atgtattgaa actggatatg cetgtteett tttacteete cetttggeat tteettttt tttetgtaag ataateatag 692 aaatttaggt aatggcggga ctacaaagat cacatggctt tatgggcccg cctattatgc 752 754 .tg <210> 47 <211> 859 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (23)..(715) <400> 47 cagcategga ggtegeteag ee atg gea tgg ate eet ete tte ete gge gte 52 Met Ala Trp Ile Pro Leu Phe Leu Gly Val ctt gct tac tgc aca gga tcc gtg gcc tcc tat gag ctg act cag cca 100 Leu Ala Tyr Cys Thr Gly Ser Val Ala Ser Tyr Glu Leu Thr Gln Pro cec tea gtg tee gtg tee eea gge aag aca gee age ate ace tge tet 148 Pro Ser Val Ser Val Ser Pro Gly Lys Thr Ala Ser Ile Thr Cys Ser 30 gga gat aaa ttg ggg gat aaa tat gct tcc tgg tat cag cag aag gca 196 Gly Asp Lys Leu Gly Asp Lys Tyr Ala Ser Trp Tyr Gln Gln Lys Ala 45 ggc cag tcc ccc gtg ctg gtc atc tat cga cat agc aag cgg ccc tca 244 Gly Gln Ser Pro Val Leu Val Ile Tyr Arg His Ser Lys Arg Pro Ser 60 65

292

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Gly Ile Pro Glu Arg Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr

80

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cag Gln	gcg Ala	tgg Trp	gac Asp 110	agc Ser	agc Ser	atc Ile	gtg Val	gtg Val 115	ttc Phe	ggc Gly	gga Gly	GJÀ 333	acc Thr 120	aag Lys	ttg Leu	388
acc Thr	gtc Val	cta Leu 125	ggt Gly	cag Gln	ccc Pro	aag Lys	gct Ala 130	gcc Ala	ccc Pro	tcg Ser	gtc <b>Val</b>	act Thr 135	ctg Leu	ttc Phe	ccg Pro	436
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acc	cctca	ccc	ccca	ccac	gg g	agad	taga	ıg ct	gcag	gato	cca	ıgggg	agg	ggto	tctcct	785
cco	cacco	caa	gcat	caag	icc c	ttct	ccct	g ca	ctca	ataa	aco	ctca	áta	aata	ttctca	845
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Al	c ate a Ile 5	c ct	c gc	c ct a Le	c cto u Leo 1	ı Le	g gc u Al	t gt: a Vai	t cto	g cas u Gl: 1	n Gl	a gte y Va	c tg: l Cy:	t gc s Ala	t gag a Glu 20	102

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PCT/US01/02623 WO 01/55437

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Ile Ala Val Asn Met Thr Lys Thr Leu Pro Thr Ala Val Thr His Gly

337

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	_	tta Leu	_	_	_				-		-	~~			-		433
		gcc Ala														•	481
		tcc Ser															529
		aat Asn															577
		aaa Lys 110															625
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ttt Phe 140	gct Ala	aca Thr	caa Gln	agt Ser	aat Asn 145	gac Asp	ttt Phe	gca Ala	ttg Leu	gga Gly 150	tac Tyr	cct Pro	ata Ile	ggt Gly	aag Lys 155		721
tta Leu	att Ile	ttt Phe	att Ile	ttt Phe 160	caa Gln	gtg Val	ttt Phe	aaa Lys	aaa Lys 165	ttc Phe	aat Asn	ttt Phe	aat Asn	tta Leu 170	ttt Phe		769
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                                     Met Leu Leu Trp Val Phe Leu
caa ctg aac tac aag att cag gca att ccg act tat gaa acc gtg atg
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Gln Leu Asn Tyr Lys Ile Gln Ala Ile Pro Thr Tyr Glu Thr Val Met
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                                                 20
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Thr Phe Phe Lys Ser Phe Pro Glu Asn Cys Cys Phe Leu Asp Arg Asp
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Ile Gly Gln Ser Leu Arg Pro Leu Phe Leu Cys Leu Arg Leu His Gly
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Gln Ser His Gly Ser Thr Arg Leu Gln Ser Thr Ile Thr Thr His Trp
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gg: Gl:	a gag y Glu 210	Lys	cta Leu	gag Glu	ccc Pro	ago Ser 215	Thr	act Thr	tcc Ser	acc Thr	Ser 220	Gln	ccc Pro	cat His	ctc Leu	672
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gg Gl	a tct y Ser	gag Glu	g att	aaa Lys	aca Thr	cct Pro	act Thr	ctt Leu	gac Asp	aag Lys	ctc Leu	gct Ala	gcc Ala	gaa Glu	gga Gly	768

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1

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atc Ile	aca Thr	tct Ser	caa Gln	tgc Cys 30	tct Ser	aag Lys	cca Pro	gag Glu	tcc Ser 35	caa Gln	gaa Glu	tcc Ser	ttc Phe	tta Leu 40	agc Ser		386
														gaa Glu			434
ctat	tcaa	ac a	attt	ctta	a ag	raata	tgca	ato	gcata	ata	aggg	gttg	gag a	ataca	igaatg		494
ctac	ttta	ct a	aaat	acta	c ag	rtgta	agaa	tgt	atag	jaaa	aaag	caca	itg o	ctttg	gagac		554
ttaa	aggo	ct g	ggta	tgaa	t ca	tggc	tctg	aca	ittaa	ıcaa	acct	cacc	tc o	ctctt	taaaa	1	614
gagt	aata	at g	gattg	gtat	c to	attg	agct	ccg	rtaaa	ıcta	aaaa	ctac	ag a	agtaa	gaagg		674
<b>aa</b> aa	gccc	tt a	caaa	agct	t tg	gagg	ggga	caa	acct	gcg	gctg	agto	at g	gctc	tgact		734
ttat	ctcc	ca t	cacc	gcct	c to	taaa	agat	aaa	aagg	att	gttt	ggca	tg ç	gaget	tttta		794
ttag	gaaa	ga a	ι				•									1	805

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50	55	60	
ttt gta aaa gta ttc c Phe Val Lys Val Phe H 65	at gac cta gtc cta t a is Asp Leu Val Leu 70	gagcaggtg aatattggag	362
attgttttct ctgtaacttt	actatcatct acctatcttc	gtattttggt gagagatcat	422
gaaaccctct atcaaactct	ctttatgcag taagttataa	caaattagca ctggcttata	482
aagatatatc aaattagagt	aaaatgcaac tgaaaatatc	ataaatcatt cggtaattaa	542
tgttttctta aattcttggg	gnaagtacaa gagaagaaat	tggagatgtg cagactttaa	602

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662

722

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cat gtc tgt tta aat gac aac acg aac agc aga aaa ata gag aaa acc 386 His Val Cys Leu Asn Asp Asn Thr Asn Ser Arg Lys Ile Glu Lys Thr 35

agt aaa tca gtt gct tca tct cca tca tac cgc gag gtc tgactacctt 435 Ser Lys Ser Val Ala Ser Ser Pro Ser Tyr Arg Glu Val 50

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gag gga tgt agg tac gag aat aca gaa tac ggg tgt ttt cta tta agc
                                                                      101
Glu Gly Cys Arg Tyr Glu Asn Thr Glu Tyr Gly Cys Phe Leu Leu Ser
                     15
aca cac att aca gag att tgc aaa aat gtt aca atg ctg ctc ttc tca
                                                                      149
Thr His Ile Thr Glu Ile Cys Lys Asn Val Thr Met Leu Leu Phe Ser
                                     35
cta aac ttt ttc ttt tgg aaa ata gtc atg ttt cat aaa aat gta ata
                                                                      197
Leu Asn Phe Phe Phe Trp Lys Ile Val Met Phe His Lys Asn Val Ile
ttt ata tta aca tgt aat ggg ttt att att gtt act ttt aaa tgg att
                                                                      245
Phe Ile Leu Thr Cys Asn Gly Phe Ile Ile Val Thr Phe Lys Trp Ile
gat aaa ttt att tta aat att tct att tta att tct aac aca gta aat
                                                                      293
Asp Lys Phe Ile Leu Asn Ile Ser Ile Leu Ile Ser Asn Thr Val Asn
     75
gtt aat agc cat aat cca cat aaa caa aag ttc ttt ggg gat ctc agt
Val Asn Ser His Asn Pro His Lys Gln Lys Phe Phe Gly Asp Leu Ser
aat ttt taacagcgta aaggggtcct gagaccaaaa agtttgagaa ctgctgcaat
                                                                      397
Asn Phe
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gcg cat aag aat gtc ctg gca gca ttc agc cag tat ttt agg aat gtt Ala His Lys Asn Val Leu Ala Ala Phe Ser Gln Tyr Phe Arg Asn Val 15 20 25	159
cag cag atg cac age aga aca aaa cgt tgg atg aat cgc atc cgc atg Gln Gln Met His Ser Arg Thr Lys Arg Trp Met Asn Arg Ile Arg Met 30 35 40	207
ctt cac cat cag tta atc gtc atc act ccg cag gtg aaa tct caa aac Leu His His Gln Leu Ile Val Ile Thr Pro Gln Val Lys Ser Gln Asn · 45 50 55	255
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tct gcc cca cac cct gag tca gac gcc aca tgc caa caa cct gtc aag Ser Ala Pro His Pro Glu Ser Asp Ala Thr Cys Gln Gln Pro Val Lys 95 100 105	399
cag atg agg ctc aaa aag gcc att cat ctg aag aag ctc aat ttc ctg Gln Met Arg Leu Lys Lys Ala Ile His Leu Lys Lys Leu Asn Phe Leu 110 115 120	447
aag tca cag aaa tac gca gag caa gta tct gaa ccc aag tca gat gat Lys Ser Gln Lys Tyr Ala Glu Gln Val Ser Glu Pro Lys Ser Asp Asp 125 130 135	495
ggt ttg aca aag agg ttg gaa tct gct agt aaa aat acc cta gag aaa Gly Leu Thr Lys Arg Leu Glu Ser Ala Ser Lŷs Asn Thr Leu Glu Lys 140 145 150	543
gct agc agc caa agt gct gaa gaa aaa gaa agt gaa gaa gtc gtc agt Ala Ser Ser Gln Ser Ala Glu Glu Lys Glu Ser Glu Glu Val Val Ser 155 160 165 170	591
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gct gcc ctg gaa gac cag tcc cag aca ctt cag tcc cag aga caa tac Ala Ala Leu Glu Asp Gln Ser Gln Thr Leu Gln Ser Gln Arg Gln Tyr 190 195 200	687
gcg tgt gaa tta tgc ggg aaa cct ttt aaa cac cca agc aac ttg gag Ala Cys Glu Leu Cys Gly Lys Pro Phe Lys His Pro Ser Asn Leu Glu 205 210 215	735
ctt cac aaa cgg tct cat aca ggt aac tga t tcagtaccca caggcagaag Leu His Lys Arg Ser His Thr Gly Asn * 220 225	786

PCT/US01/02623 WO 01/55437 846 ggaaggacgt aatgcggatg ctcagacacc actggctctt cttgtttttg taagaagttt tgctgttgtt tgatgtcatt gatgatttta aacgtcgacg cggccgcgaa ttcggatcct 906 966 cgagagatet ettttttgg gtttggtggg gtatetteat categaatag atagttatat 1013 acatcatege enngeaatte caaannence eccetettt aannteg <210> 66 <211> 3283 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (180)..(1469) <400> 66 60 tgcggatgcc ccccaattga acgccttcag gtagagcgcc gtaaggcacc ggcccggaat 120 tecoggateq acceaegegt ceggagatge eggacegete etteceaget ceteceegtg 179 ctcqctaaca caqcacqqcc gcctgcaqtc tcctctctgg gagatcgcgc gggcctaag 227 Met Cys Pro Gly Ala Leu Trp Val Ala Leu Pro Leu Leu Ser Leu Leu get gge tee eta cag ggg aag eea etg dag age tgg gga ega ggg tet 275 Ala Gly Ser Leu Gln Gly Lys Pro Leu Gln Ser Trp Gly Arg Gly Ser 25 gct ggg gga aac gcc cac agc cca ctg ggg gtg cct gga ggt ggg ctg 323 Ala Gly Gly Asn Ala His Ser Pro Leu Gly Val Pro Gly Gly Leu 35 40 cct gag cac acc ttc aac ctg aag atg ttt ctg gag aac gtg aag gtg 371 Pro Glu His Thr Phe Asn Leu Lys Met Phe Leu Glu Asn Val Lys Val 55 50 gat ttc ctg cgc agc ctt aac ctg agt ggg gtc cct tcg cag gac aaa 419 Asp Phe Leu Arg Ser Leu Asn Leu Ser Gly Val Pro Ser Gln Asp Lys 65 acc agg gtg gag ccg ccg cag tac atg att gac ctg tac aac agg tac 467 Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp Leu Tyr Asn Arg Tyr 90 acq tee gat aag teg act acg eea geg tee aac att gtg egg age tte 515 Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn Ile Val Arg Ser Phe 563 age atg gaa gat gee atc tcc ata act gee aca gag gae tte eec tte Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr Glu Asp Phe Pro Phe 120 cag aag cac atc ttg ctc ttc aac atc tcc att cct agg cat gag cag 611 Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile Pro Arg His Glu Gln 130 135 659 atc acc aga gct gag ctc cga ctc tat gtc tcc tgt caa aat cac gtg

Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser Cys Gln Asn His Val

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MOOI	/3343	,												PCI	/US01	/02623
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_				gac Asp 165	_			_		_			_	-		707
-			-	gcc Ala			_									755
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_	-		_	cgc Arg		_			_			_	-			851
_	_	_		act Thr						-		-	_	_	_	899
-		-	_	ccc Pro 245				_		_				-	_	947
			_	cac His	_	_			_	_			_		_	995
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				aca Thr		_			-	_				-	_	1091
				gct Ala												1139
				agc Ser 325												1187
				tgg Trp												1235
				aag Lys												1283
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				ggc Gly												1379
atc Ile	tcc Ser	gtc Val	ctc Leu	tac Tyr	aag Lys	gat Asp	gac Asp	atg Met	Gly ggg	gtg Val	ccc Pro	acc Thr	ctc Leu	aag Lys	tac Tyr	1427

405 410 415

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684

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accatcaaaa ceggggeeet geeagtgeet teecagtgtt caggeetagg gaagaatage	180
cccatt atg cct gtt act cct gat cct tct gca gtc tct ctc ttt gtg Met Pro Val Thr Pro Asp Pro Ser Ala Val Ser Leu Phe Val 1 5 10	228
acc cca tgg cct ttg ctg cta tgt ctg ccc tgg ccc cac aga gtg cca Thr Pro Trp Pro Leu Leu Cys Leu Pro Trp Pro His Arg Val Pro 15 20 25 30	276
ggt cag agc cac cct ggc cta cat agc agg gcc ccg gtt cac agg cta Gly Gln Ser His Pro Gly Leu His Ser Arg Ala Pro Val His Arg Leu 35 40 45	324
aaa cet ggg cet cet gee agg etg caa ete eea get gea cae ege aac Lys Pro Gly Pro Pro Ala Arg Leu Gln Leu Pro Ala Ala His Arg Asn 50 55 60	372
ctg aga cat ctc agc ata ttc tag gaactagtaa tggggacgct tccgactcgc Leu Arg His Leu Ser Ile Phe * 65 70	426
tggggaaggg agatgaggge etetagetet ceatgeceag teteteatea teaaagteat	486
ttaaggcccc agcgacccca gggttcagca gcatcctgtt catcatgagc aagagggtg	545
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tgt ctc ttc ttt ctc agc aac aca tta agg aat ggt gct act tct tgc Cys Leu Phe Phe Leu Ser Asn Thr Leu Arg Asn Gly Ala Thr Ser Cys 10 15 20	102
His Trp Tyr Cys Ser Pro Asp Asp Met Gln Met Val Asp Phe Ser Ser 25 30 35	150
The Tyr Glu Arg Ile Phe Arg Pro Phe Val Phe Lys Ile Lys Gly Pro 40 45 50 55	198
gac agc ttt agg ata gac atg agc ccc atc cct gaa gac att taa tca Asp Ser Phe Arg Ile Asp Met Ser Pro Ile Pro Glu Asp Ile * 60 65 70	246
caatctagac aagctcttgt tgtaaatgag ctcaagtatc agatttggaa gtgaatgatc	306

ttttacattt ttgtcaagot tgaggttcgt gaacttggat ccaacctctt attttttgca 366
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	C02
gtg gtg cag tac cac tga ggactg ttgctgtatt gattaggaaa agagacagag Val Val Gln Tyr His * 145 150	603
taatttgcag tttgtttgat ttatactttt gtttatctac aacccaataa cagacatgag	663
ggatggccct gtctctctgg gacagagcct caaagatgat gtccatgttt tgtgtgaatg	723
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aagagaagca actgtgcccc ggagaagaga agctcgccca ttccagactg ggaaccagct	240
ttcagtgaag atg gca ggg cca gaa ctg ttg ctc gac tcc aac atc cgc Met Ala Gly Pro Glu Leu Leu Leu Asp Ser Asn Ile Arg 1 5 10	289
	337
ctc tgg gtg gtc cta ccc atc gtt atc atc act ttc ttc gta ggc atg Leu Trp Val Val Leu Pro Ile Val Ile Ile Thr Phe Phe Val Gly Met 15 20 25	
Leu Trp Val Val Leu Pro Ile Val Ile Ile Thr Phe Phe Val Gly Met	385
Leu Trp Val Val Leu Pro Ile Val Ile Ile Thr Phe Phe Val Gly Met  15 20 25  atc cgc cac tac gtg tcc atc ctg ctg cag agc gac aag aag ctc acc Ile Arg His Tyr Val Ser Ile Leu Leu Gln Ser Asp Lys Leu Thr	385

tat tat ttc aac aac cca gag gat gga ttt ttc aaa aaa act aaa cgg Tyr Tyr Phe Asn Asn Pro Glu Asp Gly Phe Phe Lys Lys Thr Lys Arg

aag gta gtg cca cct tct cct atg act gat cct act atg ttg aca gac Lys Val Val Pro Pro Ser Pro Met Thr Asp Pro Thr Met Leu Thr Asp

atg atg aaa ggg aat gta aca aat gtc ctc cct atg att ctt att ggt

100

529

577

625

WO 01/5543	7				PCT/US01/02623
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		_	•	aca acc aag Thr Thr Lys	
		g Phe Lys P	_	cag caa gga Gln Gln Gly 155	
	r Leu Asp Al			gca tcc tgg Ala Ser Trp 170	
_				ctg att ctg Leu Ile Leu 185	
		n Ser Arg M		gag cag atg Glu Gln Met	
				gct ttc aag Ala Phe Lys	<b>U U</b>
		u Thr Asp H		gca cta gat Ala Leu Asp 235	
	u Leu Met Gl	_		cga agg cat Arg Arg His 250	=
	_		-	gag cag gga Glu Gln Gly 265	-
	a act tgg ag y Thr Trp Se 27	r Cys Thr	aa ccttg ta *	actttgtt tgg	agctggc 1109
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tgctcgtaac cactatattg taatttcaaa ccctgattcc atta atg ctt ttt gtt Met Leu Phe Val 1	29
gtg ttg cct tta ctg ata att gtg ttc aat att ccc atg agg gag gca Val Leu Pro Leu Leu Ile Ile Val Phe Asn Ile Pro Met Arg Glu Ala 5 10 15 20	34
gtc ttt gac ttt tta ttt atg ata aag att att aaa gtg ctt aaa gtt Val Phe Asp Phe Leu Phe Met Ile Lys Ile Ile Lys Val Leu Lys Val 25. 30 35	39;
ttt tat tgt ata gcg tgt ttt atc atc aag cag gtt tta gtt ttt taa Phe Tyr Cys Ile Ala Cys Phe Ile Ile Lys Gln Val Leu Val Phe $\star$ 40 45 50	44(
ggtaaactga tcaaaaataa taaaaggtga tgggtttatg acacttgggt ttgagagaac	500
tttaattgga gcaatatttc aagaaaatcc ttcttactgt ttttcgaaac tggtgagggg	560
cagagatgcc ccaagaacac ttctaggttt attggttcga aagaaaggac taccgggagt	620
ggttttaggc gcccctcggg caagaattaa taagggcaag aattcccgga agatttctaa	680
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ageteetgat gtettettea teaggttaag gatattttet tttatateta atttaattea	180
totaagaacg actoattaaa ttaogtataa ttotttaota cataaatgaa gttooctott	240
attectattt tactttttt ttaaattagg a atg gtt act tat ttt atc aaa Met Val Thr Tyr Phe Ile Lys 1 5	292
tgc ttt cat tat gag gtt tct ttt ctt ctt tgg ttt gct gtt gt	340
aat gat gta gac agg cca gtc tcc ctg tca ctc ttc tct tcc tat agt Asn Asp Val Asp Arg Pro Val Ser Leu Ser Leu Phe Ser Ser Tyr Ser 25 30 35	388
tta ttc tca aca tat cca gac aca tgt ccc ttg ttc aaa ctc ccc acc	436

WO 01/55437 PCT/US01/0	12623
Leu Phe Ser Thr Tyr Pro Asp Thr Cys Pro Leu Phe Lys Leu Pro Thr 40 45 50 55	
cac tta ctg tgt tgt tta gag gaa ata taa a tgtccttatt ataactgaca His Leu Leu Cys Cys Leu Glu Glu Ile * 60 65	487
aggccctacc ctgttcaatc ttactacttt tctgcctaat ctacttctct ctctctatct	547
aactcatect actcagtcat ettggettte ttgatgttee tggaatatae tggacatgtt	607
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tcaccacact tagttagatc cctcacagac ttcagatctt tactcaaagg tcaccttttt	727
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: tttcagaaaa ttaactctca ttgagtggca ttttctgact ccgggaataa aggatttttt	180
ttctaagatt gttttcttaa aattagaaga ctgatgttgt attattaaaa acaaccaact	240
	204
caccatgctt cagggtagag attcttttgt ctattgcta atg gag gat gtt aga Met Glu Asp Val Arg 1 5	294
gag aag gtc atg gct gta cct att atg ctg ttc tat ttc agc cta ctc Glu Lys Val Met Ala Val Pro Ile Met Leu Phe Tyr Phe Ser Leu Leu  10 15 20	342
tat aat tot otg ott ttt ttg aat oot att ott ttg otg agt acc acc Tyr Asn Ser Leu Leu Phe Leu Asn Pro Ile Leu Leu Leu Ser Thr Thr 25 30 35	390
cac cta ctt ctg gga gac aag gct gtg tga a agacatcctc agacgtctca His Leu Leu Gly Asp Lys Ala Val * 40 45	441
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actccataa atg agt ctt gtg ttg aat cag att gaa tta agt gag aaa Met Ser Leu Val Leu Asn Gln Ile Glu Leu Ser Glu Lys 1 5 10	408
gga atg gcg gtg aaa aat gtg gct tta gtc atc aca tgg gcc tac ggg Gly Met Ala Val Lys Asn Val Ala Leu Val Ile Thr Trp Ala Tyr Gly 15 20 25	456
ttt gtg aaa gta aca ttg agt ctc ctt gtg ttc tgt gtg tac tgc atg Phe Val Lys Val Thr Leu Ser Leu Leu Val Phe Cys Val Tyr Cys Met 30 35 40 45	504
tat gtc atc ttg cat cta agg atg tat att acc cat aaa gga gca tgc Tyr Val Ile Leu His Leu Arg Met Tyr Ile Thr His Lys Gly Ala Cys 50 55 60	552
aga cac atg agt gca tot tgg ott gcc act aac tgc otg tgg oot tgg Arg His Met Ser Ala Ser Trp Leu Ala Thr Asn Cys Leu Trp Pro Trp 65 70 75	600
ggc tgt cac tca act ttt cat ctg gaa att gag aat aat aat act att Gly Cys His Ser Thr Phe His Leu Glu Ile Glu Asn Asn Asn Thr Ile 80 85 90	648
atc ctt ctg gaa ttg tgt gca taa atgcacaggg cctggctcat aaaaagtact Ile Leu Leu Glu Leu Cys Ala * 95 100	702
cagtgagggc caggegggt ggegeaegee tgtaateeea geaetttggg aggeegaggg	762
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Phe Leu Arg Arg Leu Leu Ala Glu Glu Ser Arg Arg Ser Thr Pro Val

5 20

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Gly Arg Leu Leu Pro Val Leu Leu Gly Phe Arg Leu Val Leu Leu
25
30
389

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tgt cac acc cag cag ccg ggc tgc aag gct gcc tgc ttc gat gcc ttc

Cys His Thr Gln Gln Pro Gly Cys Lys Ala Ala Cys Phe Asp Ala Phe

55 60 65

cac ccc ctc tcc ccg ctg cgt ttc tgg gtc ttc cag gtc atc ttg gtg

His Pro Leu Ser Pro Leu Arg Phe Trp Val Phe Gln Val Ile Leu Val

70

80

gct gta ccc agc gcc ctc tat atg ggt ttc act ctg tat cac gtg atc
Ala Val Pro Ser Ala Leu Tyr Met Gly Phe Thr Leu Tyr His Val Ile
85 90 95 100

tgg cac tgg gaa tta tca gga aag ggg aag gag gag acc ctg atc . 629
Trp His Trp Glu Leu Ser Gly Lys Gly Lys Glu Glu Glu Thr Leu Ile
105 110 115

cag gga cgg gag ggc aac aca gat gtc cca ggg gct gga agc ctc agg 677 Gln Gly Arg Glu Gly Asn Thr Asp Val Pro Gly Ala Gly Ser Leu Arg 120 125 130

ctg ctc tgg gct tat gtg gct cag ctg ggg gct cgg ctt gtc ctg gag 725 Leu Leu Trp Ala Tyr Val Ala Gln Leu Gly Ala Arg Leu Val Leu Glu 135 140 145

ggg gca gcc ctg ggg ttg cag tac cac ctg tat ggg ttc cag atg ccc 773
Gly Ala Ala Leu Gly Leu Gln Tyr His Leu Tyr Gly Phe Gln Met Pro
150 150 160

agc tcc ttt gca tgt cgc cga gaa cct tgc ctt ggt agt ata acc tgc
Ser Ser Phe Ala Cys Arg Arg Glu Pro Cys Leu Gly Ser Ile Thr Cys
165 170 175 180

aat ctg tcc cgc ccc tct gag aag acc att ttc cta aag acc atg ttt 869
Asn Leu Ser Arg Pro Ser Glu Lys Thr Ile Phe Leu Lys Thr Met Phe
185 190 195

gga gtc agc ggt ttc tgt ctc ttg ttt act ttt ttg gag ctt gtg ctt 917 Gly Val Ser Gly Phe Cys Leu Leu Phe Thr Phe Leu Glu Leu Val Leu 200 205 210

ggt Gly									965
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cct Pro	_		_			_	_	 _	1157
gca Ala	_	-	_						1193

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480

gtg ttc ctg tcg ggt ctg ccg ccc cca gcg gag ccc gag ccc gag

Val Phe Leu Ser Gly Leu Pro Pro Pro Pro Ala Glu Pro Glu Pro Glu

WO 01/33437			
65	70	75	

		65					70					75				
ccc Pro	gaa Glu 80	ccc Pro	gaa Glu	cct Pro	gaa Glu	cct Pro 85	gcg Ala	ctg Leu	gac Asp	ctc Leu	gcg Ala 90	gcg Ala	ctg Leu	cgt Arg	gcg Ala	528
gtc Val 95	gcc Ala	tgc Cys	gac Asp	tgc Cys	ctg Leu 100	ctg Leu	cag Gln	gag Glu	cac His	ttc Phe 105	tac Tyr	ctg Leu	cgg Arg	cgc Arg	agg Arg 110	576
cgg Arg	cgc Arg	gtg Val	cac His	cgt Arg 115	tac Tyr	gag Glu	gag Glu	agc Ser	gag Glu 120	gtc Val	ata Ile	tct Ser	ttg Leu	ccc Pro 125	ttc Phe	624
ctg Leu	gat Asp	cag Gln	ctg Leu 130	gtg Val	tca Ser	acc Thr	ctc Leu	gtg Val 135	ggc Gly	ctc Leu	ctc Leu	agc Ser	cca Pro 140	cac His	aac Asn	672
ccg Pro	gcc Ala	ctg Leu 145	gcc Ala	gct Ala	gcc Ala	gcc Ala	ctc Leu 150	gat Asp	tat Tyr	aga Arg	tgc Cys	cca Pro 155	gtt Val	cat His	ttt Phe	720
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cga Arg 175	att Ile	gat Asp	gac Asp	ttg Leu	cga Arg 180	tac Tyr	cag Gln	ata Ile	gat Asp	gat Asp 185	rys	cca Pro	aac Asn	aac Asn	cag Gln 190	816
att Ile	cga Arg	ata Ile	tcc Ser	aag Lys 195	caa Gln	ctc Leu	gca Ala	gag Glu	ttt Phe 200	Val	cca Pro	ttg Leu	gat Asp	tat Tyr 205	ser	864
gtt Val	cct Pro	ata Ile	gaa Glu 210	Ile	ccc Pro	act Thr	ata Ile	aaa Lys 215	Cys	aaa Lys	cca Pro	gac Asp	aaa Lys 220	Let	cca Pro	912
tta Leu	tto Phe	aaa Lys 225	Arg	cag Glr	, tat Tyr	gaa Glu	aac Asn 230	His	ata Ile	ttt Phe	gtt Val	ggc Gly 235	ser	aaa Lys	act Thr	960
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gaa Glu	a gtt u Val	gt L Va	t ttt l Phe	aga 27:	g Ala	aat Asr	gct Ala	att a Ile	gca Ala 280	a Se	c ct	t tti u Phe	e Ala	tgg Trj 28	g act p Thr 5	1104
gga	a gca y Ala	a ca a Gl	a gci n Ala 29	a Me	g tat t Ty	caa Gli	a gga n Gly	29!	e Tr	g ag p Se	t ga r Gl	a gca u Ala	a gat a Asp 30	o Va	t act l Thr	1152
cg: Ar	a cc	t tt o Ph 30	e Va	c tc l Se	c caq r Gli	g gc	t gtg a Val	lIl	c ac	a ga r As	t gg p Gl	a aa y Ly 31	s Ty	c tt r Ph	t tcc e Ser	1200
tt: Ph	t tt e Ph	c tg e Cy	c ta	c ca r Gl	g cta n Lei	a aa u Asi	t act	t tt	g gc u Al	a ct a Le	g ac u Th	t ac	a ca r Gl	a gc n Al	t gat a Asp	1248

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320 325 330	
Caa aat aac cct cgt aaa aat ata tgt tgg ggt aca caa agt aag cct Gln Asn Asn Pro Arg Lys Asn Ile Cys Trp Gly Thr Gln Ser Lys Pro 335 340 345 350	1296
ctt tat gaa aca att gag gat aat gat gtg aaa ggt ttt aat gat g	1344
gtt cta ctt cag ata gtt cac ttt cta ctg aat aga cca aaa gaa gaa Val Leu Leu Gln Ile Val His Phe Leu Leu Asn Arg Pro Lys Glu Glu 370 375 380	1392
aaa tca cag ctg ttg gaa aac tg aaaaagcata tttgattgag aactgtggga Lys Ser Gln Leu Leu Glu Asn 385	1445
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cacaaatgtg ttcagaagtt ttacttgtga tagcaaaaat taaaaacaag tcgacttttc	780
atcaacagat aaatatgaaa acacattatg atatatgcat acaataaatt ccactctaca	840
ataaaaaaat aatacatttg gtacattcca ctacacga atg agt ctc aaa aga Met Ser Leu Lys Arg 1 5	893
att att ctg aga aaa gat tta aga ttt aaa aaa agt atc aca ctg cat Ile Ile Leu Arg Lys Asp Leu Arg Phe Lys Lys Ser Ile Thr Leu His 10 15 20	941
gaa caa ttt cat gta ttt aaa ttc tac aaa aag aca caa acc agt agc Glu Gln Phe His Val Phe Lys Phe Tyr Lys Lys Thr Gln Thr Ser Ser 25 30 35	989
gtg att gtt gag ggg agg aga aga ggg agg tat tac aaa ggg aca tgt Val Ile Val Glu Gly Arg Arg Arg Gly Arg Tyr Tyr Lys Gly Thr Cys 40 45 50	1037
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Met Phe Lys Val Val Phe Cys Phe Gly Leu Val Trp Phe Cys Phe Gln 1 5 10 15	
agg gca cac aaa cca atc cga ttt gaa aaa cac aac ttt aca ata aat Arg Ala His Lys Pro Ile Arg Phe Glu Lys His Asn Phe Thr Ile Asn 20 25 30	215
gaa gga aac ctg ttc tct atg aat atc cca att gta acg att agg tct Glu Gly Asn Leu Phe Ser Met Asn Ile Pro Ile Val Thr Ile Arg Ser 35 40 45	263
cac cac agg aca agt tgc tac cac aaa tta atc aca tgt gaa cag caa His His Arg Thr Ser Cys Tyr His Lys Leu Ile Thr Cys Glu Gln Gln	311

PCT/US01/02623 WO 01/55437 - 360 act gtc ttt acg aac ata aag agg cat tct aag ttg tag cagacgcctg Thr Val Phe Thr Asn Ile Lys Arg His Ser Lys Leu \* ctctacgaga cattaatgga gtaaaatcct ggagtattac agataaacag ttaaagtgat 420 gaacaagggc tttatggttt gtataaacag aaatataaac aattttgtat ttttctcaat 480 tatatgtaat taaataacgt ttcagggtaa caaagtattg ggtccctttt tttaccagct 540 tattctaaag aggctttgaa taaaggaaat tttgtttctt gcctccaaga aagagccccc 600 eccecece tecaaatttt gatagaaaaa aaatttgnee agageetega eeeeeeeee 659 <210> 83 <211> 653 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (147) .. (308) ccggtccgga attcccgggt cgacccacgc gtccgatttc ctaaaacttt attcctctaa 60 acatettete aatteeceag atettgtttt agttgtagag geecaaagta gageteteta 120 aacaaagget teeteagtge tgtaaa atg aat ttg tat ete ttt get gtt ete 173 Met Asn Leu Tyr Leu Phe Ala Val Leu 1 221 ttc ttt tat gta ttt cta cat ata aaa atc atc ttt att tgt ttt gct Phe Phe Tyr Val Phe Leu His Ile Lys Ile Ile Phe Ile Cys Phe Ala 15 10 269 act aaa tgg cat aat tta ttt tcg aaa ttc agt tat ttt tgt att ttg Thr Lys Trp His Asn Leu Phe Ser Lys Phe Ser Tyr Phe Cys Ile Leu 30 cat gtt aag gct cta agc ctt aac tta ggg tct ggg taa atatgaactc 318 His Val Lys Ala Leu Ser Leu Asn Leu Gly Ser Gly \* caagacteet egaaaatagt gtagaaataa tagcaaaatt aaagatgttt gtatteeetg 378 438 tgaatttatt ttttctttca ttcaacacag aatgtgtatc tagtacgtgc taggcattat aaatttagca gtgaacaaag atgataaaat ctcagctctc ctggagccaa cgttctagtg 498 558 aaaaatttct ctttcttcta ctttttctgt tgacattcat atgggctaac aatgtacccc gagggctggg gattataaag gagaagaaag gtgggggacc cggctcagct ggtaaaatgg 618

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gaatggaatg accecettaa eccagaaace ttett

653

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tttttcttca ttttttatgg aatgtaaagc tcatcc atg tgt aca tta ttc atg Met Cys Thr Leu Phe Met 1 5	174
cat tta ctt ttc tgc cac ctc caa agc att caa tta aag cag gaa tta His Leu Leu Phe Cys His Leu Gln Ser Ile Gln Leu Lys Gln Glu Leu 10 15 20	222
agg ctc aac tat ctt act tta aca cag ttt tgg cag aga tgt tac agt Arg Leu Asn Tyr Leu Thr Leu Thr Gln Phe Trp Gln Arg Cys Tyr Ser 25 30 35	270
gag atg att ttt ttc tgt ctg tca aag gtg ttt ctt cat gtt ttc caa Glu Met Ile Phe Phe Cys Leu Ser Lys Val Phe Leu His Val Phe Gln 40 45 50	318
gat ggt cta gaa cat cat tta gag taa atttt cattttggag gaaattttta Asp Gly Leu Glu His His Leu Glu * 55 60	370
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aaaagcccaa agggaaaaaa taagtttctt actctgactt tcacacatac tgtgttctat	490
ttgctccctt catatgtccc agagctaact cctcttcact gagaacgagg gcttaatttg	550
aatggtttta atgcctttta accttttaaa atttttatgg acaatttaac tggcattttt	610
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<212> DNA

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catggaaget cetgaggage eegegeeagt gegeggagge eeggaggeea eeettgaggt 180
cegtgggteg egetgettge ggetgteege etteegagaa gagetgeggg egetettggt 240
cetggetgge eeegegttet tggtteaget gatggtgte etgateaget teataagete 300
egtgttetgt ggeeacctgg geaagetgga getggatgea gteacgetgg caategeggt 360
tateaatgte actggtgtet eagtgggatt eggettatet tetgeetgtg acaeceteat 420

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getegteetg etectetget getteecetg etgggegett titetaacae titeacatee	
tgctgctctt caggcaggac ccagatgtgt ccaggcttac ccagacctat gtcacgatct	
tcattccagc tcttcctgca acctttcttt at atg tta caa gtt aaa tat ttg Met Leu Gln Val Lys Tyr Leu 1 5	653
ctc aac cag gga att gta ctg ccc cag atc gta act gga gtt gca gcc Leu Asn Gln Gly Ile Val Leu Pro Gln Ile Val Thr Gly Val Ala Ala 10 15 20	701
aac ctt gtc aat gcc ctc gcc aac tat ctg ttt ctc cat caa ctg cat Asn Leu Val Asn Ala Leu Ala Asn Tyr Leu Phe Leu His Gln Leu His 25 30 35	749
ctt ggg gtg ata ggc tct gca ctg gca aac ttg att tcc cag tac acc Leu Gly Val Ile Gly Ser Ala Leu Ala Asn Leu Ile Ser Gln Tyr Thr 40 45 50 55	797
ctg gct cta ctc ctc ttt ctc tac atc ctc ggg aaa aaa ctg cat caa Leu Ala Leu Leu Phe Leu Tyr Ile Leu Gly Lys Lys Leu His Gln 60 65 70	845
gct aca tgg gga ggc tgg tcc ctc gag tgc ctg cag gac tgt gcc tcc Ala Thr Trp Gly Gly Trp Ser Leu Glu Cys Leu Gln Asp Cys Ala Ser 75 80 85	893
ttc ctc cgc ctg gcc atc ccc agc atg ctc atg ctg tgc atg gag tgg Phe Leu Arg Leu Ala Ile Pro Ser Met Leu Met Leu Cys Met Glu Trp 90 95 100	941
tgg gcc tat gag gtc ggg agc ttc ctc agt ggc atc ctc ggc atg gtg Trp Ala Tyr Glu Val Gly Ser Phe Leu Ser Gly Ile Leu Gly Met Val 105 110 115	989
gag ctg ggc gct cag tcc atc gtg tat gaa ctg gcc atc att gtg tac Glu Leu Gly Ala Gln Ser Ile Val Tyr Glu Leu Ala Ile Ile Val Tyr 120 125 130 135	1037
atg gtc cct gca ggc ttc agt gtg gct gcc agt gtc cgg gta gga aac Met Val Pro Ala Gly Phe Ser Val Ala Ala Ser Val Arg Val Gly Asn 140 145 150	1085
gct ctg ggt gct gga gac atg gag cag gca cgg aag tcc tct acc gtt Ala Leu Gly Ala Gly Asp Met Glu Gln Ala Arg Lys Ser Ser Thr Val 155 160 165	1133
too otg otg att aca gtg oto ttt got gta goo tto agt gto ota otg Ser Leu Leu Ile Thr Val Leu Phe Ala Val Ala Phe Ser Val Leu Leu 170 175 180	1181
tta agc tgt aag gat cac gtg ggg tac att ttt act acc gac cga gac Leu Ser Cys Lys Asp His Val Gly Tyr Ile Phe Thr Thr Asp Arg Asp 185 190 195	•
atc att aat ctg gtg gct cag gtg gtt cca att tat gct gtt tcc cad Ile Ile Asn Leu Val Ala Gln Val Val Pro Ile Tyr Ala Val Ser His 200 205 210	5
ctc ttt gaa gct ctt gct tgc acg agt ggt ggt gtt ctg agg ggg ag Leu Phe Glu Ala Leu Ala Cys Thr Ser Gly Gly Val Leu Arg Gly Se	1325

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220 225	230
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gct ggc ctc ccc atc ggg atc gcg ctg atg ttt gca acc aca Ala Gly Leu Pro Ile Gly Ile Ala Leu Met Phe Ala Thr Thr 250 255 260	ctt gga 1421 Leu Gly
gtg atg ggt ctg tgg tca ggg atc atc atc tgt aca gtc ttt Val Met Gly Leu Trp Ser Gly Ile Ile Ile Cys Thr Val Phe 265 270 275	caa gct 1469 Gln Ala
gtg tgt ttt cta ggc ttt att att cag cta aat tgg aaa aaa Val Cys Phe Leu Gly Phe Ile Ile Gln Leu Asn Trp Lys Lys 280 285 290	gcc tgt 1517 Ala Cys 295
cag cag ggt gcc ctg aaa acc ttg aag gaa ttt taa cgaa cg	atgttgga 1567
aagacaggcg agcctcagtc agatcagcag atgcgccaag aagaaccttt g	ccggaacat 1627
ccacaggacg gcgctaaatt gtccaggaaa cagctggtgc tgcggcgagg g	cttctgctc 1687
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atg cga agt aca aaa ctg ctt cgg ctc att gac tta gat ttt tca ttt Met Arg Ser Thr Lys Leu Leu Arg Leu Ile Asp Leu Asp Phe Ser Phe 35 40 45	324
act ttc tct ctc ttg gat cta cca cca gta aat gaa tat gac atg tat Thr Phe Ser Leu Leu Asp Leu Pro Pro Val Asn Glu Tyr Asp Met Tyr 50 60	372
atc aga aac ttt gga aaa aaa aaa agg ggg ggc cgt ttt aaa gga Ile Arg Asn Phe Gly Lys Lys Lys Lys Arg Gly Gly Arg Phe Lys Gly 65 70 75 80	420
tcc agg ttt acg aac gcg ggc tgg caa cgt aaa agt ttt ttt atg ggg Ser Arg Phe Thr Asn Ala Gly Trp Gln Arg Lys Ser Phe Phe Met Gly 85 90 95	468
ccc cct aaa tcc att cca ggg gcc ggg gtt taa caacgggg ggacgggaaa Pro Pro Lys Ser Ile Pro Gly Ala Gly Val * 100 105	519
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ncaaaaatca ttacatttne ceenacnace aaaatecace teteceetee ecaatnnnee	819
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220

268

cetectgetg ceaggeace atg aca gtg agg ggg gat gtg etg gee eeg gat Met Thr Val Arg Gly Asp Val Leu Ala Pro Asp

cca gcg tcg ccc acg acc gca gca gcc tcg ccc agc gtc tcc gtg atc

Pro Ala Ser Pro Thr Thr Ala Ala Ser Pro Ser Val Ser Val Ile 20

ccc gag ggc agc ccc act gcc atg gag cag cct gtg ttc ctg atg aca

atc aca tgc cac cag atc tac atg cac ctg cgc tgc tac agc tgc ccc

Ile Thr Cys His Gln Ile Tyr Met His Leu Arg Cys Tyr Ser Cys Pro

60

65

70

75

aac gag cag cgc tac atc gtg cgc atc ctc ttc atc gtg ccc atc tac
Asn Glu Gln Arg Tyr Ile Val Arg Ile Leu Phe Ile Val Pro Ile Tyr
80 85

gcc ttt gac tcc tgg ctc agc ctc ctc ttc ttc acc aac gac cag tac
Ala Phe Asp Ser Trp Leu Ser Leu Leu Phe Phe Thr Asn Asp Gln Tyr
95 100 105

tac gtg tac ttc ggc acc gtc cgc gac tgc tat gag gcc ttg gtc atc

Tyr Val Tyr Phe Gly Thr Val Arg Asp Cys Tyr Glu Ala Leu Val Ile

110 115 120

tat aat ttc ctg agc ctg tgc tat gag tac cta gga gga gaa agt tcc
Tyr Asn Phe Leu Ser Leu Cys Tyr Glu Tyr Leu Gly Gly Glu Ser Ser
125 130 135

atc atg tcg gag atc aga gga aaa ccc att gag tcc agc tgt atg tat 604

Ile Met Ser Glu Ile Arg Gly Lys Pro Ile Glu Ser Ser Cys Met Tyr

145 150 155

ggc acc tgc tgc ctc tgg gga aag act tat tcc atc gga ttt ctg agg 652 Gly Thr Cys Cys Leu Trp Gly Lys Thr Tyr Ser Ile Gly Phe Leu Arg 160 165 170

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Phe Cys Lys Gln Ala Thr Leu Gln Phe Cys Val Val Lys Pro Leu Met
175 180 185

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Ala Val Ser Thr Val Val Leu Gln Ala Phe Gly Lys Tyr Arg Asp Gly
190
195
200

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Asp Phe Asp Val Thr Ser Gly Tyr Leu Tyr Val Thr Ile Ile Tyr Asn
205 210 215

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Ile Ser Val Ser Leu Ala Leu Tyr Ala Leu Phe Leu Phe Tyr Phe Ala

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acc cgg gag ctg ctc agc ccc tac agc ccc gtc ctc aag ttc ttc atg

Thr Arg Glu Leu Leu Ser Pro Tyr Ser Pro Val Leu Lys Phe Phe Met

240

245

gtc aag tcc gtc atc ttt ctt tcc ttc tgg caa ggc atg ctc ctg gcc 940 Val Lys Ser Val Ile Phe Leu Ser Phe Trp Gln Gly Met Leu Leu Ala 255 260 265

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Ile Leu Glu Lys Cys Gly Ala Ile Pro Lys Ile His Ser Ala Arg Val
270

275

280

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cta cct cag cct cct gag tag ct gggactgcaa gtgtatacca ctatgcctgg Leu Pro Gln Pro Pro Glu * 95	585
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agatttaatt ttttaaatgt catttttctt gcatctcatc aaatatactt tcatacacta  taaaa atg atg ttg ggt cat atg tat cac atg tct gta att cag aaa  Met Met Leu Gly His Met Tyr His Met Ser Val Ile Gln Lys  1 5 10	120 167
taaaa atg atg ttg ggt cat atg tat cac atg tct gta att cag aaa Met Met Leu Gly His Met Tyr His Met Ser Val Ile Gln Lys	
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Ala Leu \*

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Ser Ser Ala Val Leu Gln Ile Thr Pro Val Asp Thr Phe Ser Asp Pro
35
40
45

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His Leu Val Leu Thr Leu Val Lys Leu Leu Met Asn Ile Leu Asn Ile
50 55 60

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Phe Glu Asn Ile Leu Met Tyr Thr His Ala Phe Ile Ile Cys Phe Cys

80

85

90

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WO 01/55437			PCT/US01/02623
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cac ata aaa gct His Ile Lys Ala	ttg caa act gtg Leu Gln Thr Val	g acc tcc ttt ctt o L Thr Ser Phe Leu 1 25	ctg tta tgt gcc 216 Leu Leu Cys Ala 30
att tac ttt ctg Ile Tyr Phe Leu 35	Ser Met Ile Ile	a tca gtt tgt aat ( e Ser Val Cys Asn ) 40	ttt ggg agg ctg 264 Phe Gly Arg Leu 45
		c tgc caa gct att a e Cys Gln Ala Ile : 5	
		g att ttg gga aac a u Ile Leu Gly Asn 1 75	

cag att ttt ctt tca gtt ttg cgg cat gtg agg tac tgg gtg aaa gac Gln Ile Phe Leu Ser Val Leu Arg His Val Arg Tyr Trp Val Lys Asp 80 85 90 95

aga agc ctt cgt ctc ca Arg Ser Leu Arg Leu Hi 100			456
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103

tgg ctc acg ctg acc gcc gcc ttc ctg ctg acc cta ctg ctg cag ctc Trp Leu Thr Leu Thr Ala Ala Phe Leu Leu Thr Leu Leu Gln Leu 151

199

55

ctg ccg ccc ggc ctg ctc ccg ggc tgc gcg atc ttc cag gac ctg atc Leu Pro Pro Gly Leu Leu Pro Gly Cys Ala Ile Phe Gln Asp Leu Ile

247

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cga gcc ttt gat gtc ccc aag aga tat ttt tcc cac ttt tat atc atc Arg Ala Phe Asp Val Pro Lys Arg Tyr Phe Ser His Phe Tyr Ile Ile

295

343

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391

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ctc ggg gcg gca cag ttc cag gga ggg gag ctg gca ctg tct gca ttc Leu Gly Ala Ala Gln Phe Gln Gly Gly Glu Leu Ala Leu Ser Ala Phe 115 120 125 130	439
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cca ttt gga gac tgg ttt gaa tat gtt tct tcc cct aac tac tta gca Pro Phe Gly Asp Trp Phe Glu Tyr Val Ser Ser Pro Asn Tyr Leu Ala 245 250 255	823
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tta act tgg tgg cta gtg gtg aca aat gtc ttc ttt aat cag gcc ctg Leu Thr Trp Trp Leu Val Val Thr Asn Val Phe Phe Asn Gln Ala Leu 275 280 285 290	919
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ccg ccg acg ttc ggc caa ggg acc aag gtg gaa atc aaa cga act gtg Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val 245 250 255 260	941
gct gca cca tct gtc ttc atc ttc ccg cca tct gat gag cag ttg aaa Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys 265 270 275	989
Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg 280 285 290	1037
gag gcc aaa gta cag tgg aag gtg gat aac gcc ctc cca atc ggg taa Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Pro Ile Gly * 295 300 305	1085
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60

413

gaa att att agt agc ggt ggt acc aca tac tac gca gac tcc gtg aag

Glu Ile Ile Ser Ser Gly Gly Thr Thr Tyr Tyr Ala Asp Ser Val Lys

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	u Val Thr	_	er Gly Asp	ggg tcc ag Gly Ser Se		-
				acg cag to Thr Gln Se 160		
	_			tete tee te Leu Ser Cy 175		•
		-		tac cag cag cag Tyr Gln Gl	-	
				tcc agc ag Ser Ser A		
	p Arg Phe		er Gly Ser	ggg aca ga Gly Thr As		
				gca gtg ta Ala Val Ty 240		
cag acg gg Gln Thr Gl 245	t cgt att y Arg Ile	ccg ccg ac Pro Pro Th 250	cg ttc ggd hr Phe Gly	caa ggg ao Gln Gly Ti 255	cc aag gtg hr Lys Val	gaa 941 Glu 260
				ttc atc to Phe Ile Ph		
gat gag ca Asp Glu Gl	g ttg aaa n Leu Lys 280	tct gga ac Ser Gly Th	ct gcc tct nr Ala Ser 285	gtt gtg tg Val Val C	gc ctg ctg ys Leu Leu 290	aat 1037 Asn
aac ttc ta Asn Phe Ty 29	r Pro Arg	gag gcc aa Glu Ala Ly 30	ys Val Glr	tgg aag gt Trp Lys Va	tg gat aac al Asp Asn 05	gcc 1085 Ala
ctc cca at Leu Pro Il 310		ctcccaggag	g agtgtcac	ag agcagga	cag caaggad	cagc 1140

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1680

1736

509

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	gac Asp															701
	ctg Leu	-			_	-					_		_		_	749
	tat Tyr															797
	agt Ser															845
	gat Asp 230	-		-				_	_			_			-	. 893
	act Thr															941
	cca Pro						_			_		_	_			989
	act Thr															1037
-	aaa Lys	_	_		-		_		_			_				1085
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267 aac ata qtt aaa qca aqa att qaq agt aca aag aca gtg ata tca aag Asn Ile Val Lys Ala Arg Ile Glu Ser Thr Lys Thr Val Ile Ser Lys

20

aga tgt taa teeteea cacagtetgg etgeattgag gatatttete tttgtgeagt 323 Arg Cys \*

agaaaactgg aaatagctaa gtctattgga actcttcttt ctcaaattct attgaactga 383 443 agagtaggaa atttagaaac agtaagacgt gggagataat ttaactgaat tcactacttt

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aggtgtgatg cctgaaaagg gactgatata actgagc atg gct atg cag tct gtg	235
Met Ala Met Gln Ser Val	
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Ile Arg Lys Gln Phe Thr Ala Leu Ala Gly Phe Cys Phe Trp Phe Cys	263
10 15 20	
ctc ttt acc tta gca gtc ctg agt ctc acc ttg ctt atc tgc aaa ctg	331
Leu Phe Thr Leu Ala Val Leu Ser Leu Thr Leu Leu Ile Cys Lys Leu	
25 30 35	
agg ata atg cca ttt aaa ctt gaa ggt ttg ttt caa gaa tta aat aaa	379
Arg Ile Met Pro Phe Lys Leu Glu Gly Leu Phe Gln Glu Leu Asn Lys	3,,
40 45 50	
tca tgg cat atg aag ctc ttg tca caa gat agg gag tta ata aat atg	427
Ser Trp His Met Lys Leu Ser Gln Asp Arg Glu Leu Ile Asn Met	
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Leu Leu Leu Met Gly Arg Ser *	
75	
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ggc Gly 35	tcc Ser	agg Arg	acc Thr	gcc Ala	ttc Phe 40	ttt Phe	ggc Gly	tac Tyr	aca Thr	gtg Val 45	cag Gln	cag Gln	cac His	gac Asp	atc Ile 50		201
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tac Tyr	cag Gln	aag Lys	acg Thr 70	gga Gly	gac Asp	gtg Val	tac Tyr	aag Lys 75	tgt Cys	cca Pro	gtg Val	atc Ile	cac His 80	Gly ggg	aac Asn		297
tgc Cys	acc Thr	aaa Lys 85	ctc Leu	aac Asn	ctg Leu	gga Gly	agg Arg 90	gtc Val	acc Thr	ctg Leu	tcc Ser	aac Asn 95	gtg Val	tcc Ser	gag Glu	٠	345
cgg Arg	aaa Lys 100	gac Asp	aac Asn	atg Met	cgc Arg	ctc Leu 105	ggc Gly	ctt Leu	agt Ser	ctc Leu	gcc Ala 110	acc Thr	aac Asn	ccc Pro	aag Lys		393
gac Asp 115	aac Asn	agc Ser	ttc Phe	ctg Leu	gcc Ala 120	tgc Cys	agc Ser	ccc Pro	ctc Leu	tgg Trp 125	tct Ser	cat His	gag Glu	tgt Cys	339 130		441
agc Ser	tcc Ser	tac Tyr	tac Tyr	acc Thr 135	aca Thr	Gly	atg Met	tgt Cys	tca Ser 140	aga Arg	gtc Val	aac Asn	tcc Ser	aac Asn 145	ttc Phe		489
agg Arg	ttc Phe	tcc Ser	aag Lys 150	acc Thr	gtg Val	gcc Ala	cca Pro	gct Ala 155	ctc Leu	caa Gln	agg Arg	tgc Cys	cag Gln 160	acc Thr	tac Tyr		537
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											ttc Phe						825
											aca Thr						873

260 265 270

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	gac Asp															921
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	aac Asn	_							_		_		_	_		1161
	tcc Ser	_					_		_	_	_		_	-		1209
	tat Tyr															1257
-	att Ile			_				_								1305
_	aac Asn 420			_		_				_		_	_			1353
	agg Arg	_		_				_		_						1401
_	ggc Gly	_	_		_			-					_			1449
	cac His															1497
gaa Glu	atc Ile	acc Thr 485	tcg Ser	gtg Val	gac Asp	atc Ile	gac Asp 490	ggc Gly	gac Asp	ggc	gtg Val	act Thr 495	gat Asp	gtc Val	ctg Leu	1545
	gtg Val 500		-		_						_		_		_	1593
	tac Tyr															1641

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515		520			525					530	
cta aag gat Leu Lys Asp	tca cac Ser His 535	agt tac Ser Tyr	cag aat Gln Asn	gcc Ala 540	cga Arg	ttt Phe	gly aaa	tcc Ser	tcc Ser 545	att Ile	1689
gcc tca gtt Ala Ser Val	cga gac Arg Asp 550	ctc aac Leu Asn	cag gat Gln Asp 555	tcc Ser	tac Tyr	aat Asn	gac Asp	gtg Val 560	gtg Val	gtg Val	1737
gga gcc ccc Gly Ala Pro 569	Leu Glu	gac aac Asp Asn	cac gca His Ala 570	gga Gly	gcc Ala	Ile	tac Tyr 575	atc Ile	ttc Phe	cac His	1785
ggc ttc cga Gly Phe Arg 580	a ggc agc g Gly Ser	atc ctg Ile Leu 585	aag aca Lys Thr	cct Pro	Lys	cag Gln 590	aga Arg	atc Ile	aca Thr	gcc Ala	1833
tca gag cto Ser Glu Leo 595	g gct acc 1 Ala Thr	ggc ctc Gly Leu 600	cag tat Gln Tyr	Phe	ggc Gly 605	tgc Cys	agc Ser	atc Ile	cac His	ggg 610	1881
caa ttg gad Gln Leu As	ctc aat Leu Asn 615	Glu Asp	ggg ctc Gly Leu	atc Ile 620	gac Asp	ctg Leu	gca Ala	gtg Val	gga Gly 625	gcc Ala	1929
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tgc aag cg Cys Lys Ar 660	c agt ggo g Ser Gly	agg gat Arg Asp 665	Ala Thr	tgc Cys	ctg Leu	gcc Ala 670	gcc Ala	ttc Phe	ctc Leu	tgc Cys	2073
ttc acg cc Phe Thr Pr 675	c atc tto o Ile Phe	ctg gca Leu Ala 680	ccc cat Pro His	ttc Phe	caa Gln 685	aca Thr	aca Thr	act Thr	gtt Val	ggc 690	2121
atc aga ta Ile Arg Ty	c aac gco r Asn Ala 699	Thr Met	gat gag Asp Glu	agg Arg 700	cgg Arg	tat Tyr	aca Thr	ccg Pro	agg Arg 705	gcc Ala	2169
cac ctg ga His Leu As	c gag ggc p Glu Gly 710	ggg gad Gly Asp	cga tto Arg Phe 715	Thr	aac Asn	aga Arg	gcc Ala	gta Val 720	ctg Leu	ctc Leu	2217
tcc tcc gg Ser Ser Gl 72	y Gln Glu	g ctc tgt 1 Leu Cys	gag cgg Glu Arg 730	atc Ile	aac Asn	ttc Phe	cat His 735	gtc Val	ctg Leu	gac Asp	2265
act gct ga Thr Ala As 740	c tac gtg p Tyr Val	g aag cca L Lys Pro 745	Val Thr	ttc Phe	tca Ser	gtc Val 750	gag Glu	tat Tyr	tcc Ser	ctg Leu	2313
gag gac co Glu Asp Pr 755	t gac cat o Asp His	ggc ccc Gly Pro 760	atg ctg Met Leu	gac Asp	gac Asp 765	ggc Gly	tgg Trp	ccc Pro	acc Thr	act Thr 770	2361
ctc aga gt Leu Arg Va	c tcg gtg l Ser Val	g ccc tto L Pro Phe	tgg aac Trp Asr	ggc Gly	tgc Cys	aat Asn	gag Glu	gat Asp	gag Glu	cac His	2409

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tgt gtc cct gac Cys Val Pro Asp 790				
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cgc cag cga gtg Arg Gln Arg Val 835				
gcc tac agc acg Ala Tyr Ser Thr				
gcc agc ttg atc Ala Ser Leu Ile 870	Gln Lys Glu As			
aac gag. gag agg Asn Glu Glu Arg 885	Arg Leu Gln Ly			
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agt gac agt aat Ser Asp Ser Asn	gag cgg gac ag Glu Arg Asp Se 935	gc acc aag gaa g er Thr Lys Glu <i>I</i> 940	gac aac gtg gcc Asp Asn Val Ala 945	ccc 2889 Pro
tta cgc ttc cac Leu Arg Phe His 950	ctc aaa tac ga Leu Lys Tyr Gl	ag gct gac gtc o lu Ala Asp Val I 955	ctc ttc acc agg Leu Phe Thr Arg 960	agc 2937 Ser
agc agc ctg agc Ser Ser Leu Ser 965	His Tyr Glu Va	tc aag ccc aac a al Lys Pro Asn 8 70	agc tcg ctg gag Ser Ser Leu Glu 975	aga 2985 Arg
tac gat ggt atc Tyr Asp Gly Ile 980	ggg cct ccc tt Gly Pro Pro Pr 985	he Ser Cys Ile I	ttc agg atc cag Phe Arg Ile Gln 990	aac 3033 Asn
ttg ggc ttg ttc Leu Gly Leu Phe 995	Pro Ile His Gl	gg atg atg atg a ly Met Met Met I 1005	Lys Ile Thr Ile	ccc 3081 Pro 1010
	Ser Gly Asn Ar 1015	rg Leu Leu Lys I 1020	Leu Arg Asp Phe 1025	Leu
acg gac gag gcg Thr Asp Glu Ala	aac acg tcc tg Asn Thr Ser Cy	gt aac atc tgg g ys Asn Ile Trp G	ggc aat agc act Gly Asn Ser Thr	gag 3177 Glu

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WD 01/55437	PC1/USU1/UZU25

WO 01/55437 1035 1040 1030 3225 tac cqq ccc acc cca gtg gag gaa gac ttg cgt cgt gct cca cag ctg Tyr Arg Pro Thr Pro Val Glu Glu Asp Leu Arg Arg Ala Pro Gln Leu 1050 1045 3273 aat cac age aac tot gat gto gto too atc aac tgo aat ata cgg ctg Asn His Ser Asn Ser Asp Val Val Ser Ile Asn Cys Asn Ile Arg Leu 1065 1070 gtc ccc aac cag gaa atc aat ttc cat cta ctg ggg aac ctg tgg ttg 3321 Val Pro Asn Gln Glu Ile Asn Phe His Leu Leu Gly Asn Leu Trp Leu 1085 1075 1080 agg tcc cta aaa gca ctc aag tac aaa tcc atg aaa atc atg gtc aac 3369 Arg Ser Leu Lys Ala Leu Lys Tyr Lys Ser Met Lys Ile Met Val Asn 1095 1100 3417 gea gee ttg eag agg eag tte eac age eec tte ate tte egt gag gag Ala Ala Leu Gln Arg Gln Phe His Ser Pro Phe Ile Phe Arg Glu Glu 1110 1115 gat ecc age ege cag ate gtg ttt gag ate tee aag caa gag gae tgg 3465 Asp Pro Ser Arg Gln Ile Val Phe Glu Ile Ser Lys Gln Glu Asp Trp 1125 1130 3513 cag gtc ccc atc tgg atc att gta ggc agc acc ctg ggg ggc ctc cta Gln Val Pro Ile Trp Ile Ile Val Gly Ser Thr Leu Gly Gly Leu Leu 1140 1145 3561 ctg ctg gcc ctg gtc ctg gca ctg tgg aag ctc ggc ttc ttt aga Leu Leu Ala Leu Leu Val Leu Ala Leu Trp Lys Leu Gly Phe Phe Arg 1160 1165 1170 1155 agt gcc agg cgc agg agg cct ggt ctg gac ccc acc ccc aaa gtg 3609 Ser Ala Arg Arg Arg Glu Pro Gly Leu Asp Pro Thr Pro Lys Val 1180 ctg gag tga ggctcca gaggagactt tgagttgatg ggggccagga caccagtcca 3665 Leu Glu \* ggtagtgttg agacccaggc ctgtggcccc accgagctgg agcggagagg aagccagctg 3725 getttqcact tqacetcate tecegageaa tggegeetge tecetecaga atggaactca 3785 agetggtttt aagtggaact geeetaetgg gagaetggga caeetttaae acagaeeeet 3845 agggatttaa agggacaccc ctacacacac ccaggcccac gccaaggcct ccctcaggct 3905

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104

Phe Pro Leu Trp Lys Leu Leu Asn Val Leu Val Cys Ile Phe Ser Ser

10

15

ttc atc atg ctg aat att tac tgt acc ctt ttg atc tgg aaa ttt att

Phe Ile Met Leu Asn Ile Tyr Cys Thr Leu Leu Ile Trp Lys Phe Ile

20

25

30

35

tat tca gct ttt ttc tgt tat att act tct ttg atg atg att ttc ccc ttt

200

Tyr Ser Ala Phe Phe Cys Tyr Ile Thr Ser Leu Met Ile Phe Pro Phe

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ctgggtccag gtggctggtc tgctgcccc aaaagcctga ccttcttggt cctgtgggtc 383
tgtcagtaag gcaggtagcc atagctggag agagacagcc accaggctgg gatcttggac 443
agtccctaca tttctgtgta atcctggact aggcagggca tggagtagat ggaaaatggc 503
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115

Thr Ala Trp Glu Ala Asn Leu Pro Lys Gly Arg His Thr His Pro Glu

tgt cta gct cct ctt ctt gtc cct tgt aaa tgt gca ttt cca ctt tac 734
Cys Leu Ala Pro Leu Leu Val Pro Cys Lys Cys Ala Phe Pro Leu Tyr
125 130 135

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Met Ala Trp Ile Pro Leu Phe Leu Gly Val

1 5 10

ctt gct tac tgc aca gga tcc gtg gcc tcc tat gag ctg act cag cca
Leu Ala Tyr Cys Thr Gly Ser Val Ala Ser Tyr Glu Leu Thr Gln Pro

15 20 25

ccc tca gtg tcc gtg tcc cca gga cag aca gcc agc atc acc tgc tct

Pro Ser Val Ser Val Ser Pro Gly Gln Thr Ala Ser Ile Thr Cys Ser

30 40

gga gat aaa ttg ggg gat aaa tat gct tgc tgg tat cag cag aag cca 254
Gly Asp Lys Leu Gly Asp Lys Tyr Ala Cys Trp Tyr Gln Gln Lys Pro
45 50 55

ggc cag tcc cct gtg ctg gtc atc tat caa gat agc aag cgg ccc tca 302
Gly Gln Ser Pro Val Leu Val Ile Tyr Gln Asp Ser Lys Arg Pro Ser
60 65 70

ggg atc cct gag cga ttc tct ggc tcc aac tct ggg aac aca gcc act
Gly Ile Pro Glu Arg Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr
75
80
85
90

ctg acc atc agc ggg acc cag gct atg gat gag gct gac tat tac tgt

198

Leu Thr Ile Ser Gly Thr Gln Ala Met Asp Glu Ala Asp Tyr Tyr Cys

100

105

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110 115 120

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Val Thr Val Leu Gly Gln Pro Lys Ala Asn Pro Thr Val Thr Leu Phe
125 130 135

ccg ccc tcc tct gag gag ctc caa gcc aac aag gcc aca cta gtg tgt 542
Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys
140 150

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Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala
155 160 165 170

gat ggc agc ccc gtc aag gcg gga gtg gag acc acc aaa ccc tcc aaa Asp Gly Ser Pro Val Lys Ala Gly Val Glu Thr Thr Lys Pro Ser Lys 175 180 185	638
cag agc aac aac aag tac gcg gcc agc agc tac ctg agc ctg acg cct Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro 190 195 200	686
gag cag tgg aag tcc cac aga agc tac agc tgc cag gtc acg cat gaa Glu Gln Trp Lys Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu 205 210 215	734
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ctaaaccete acctececce acgggagact agagetgeag gateceaggg gaggggtete	842
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aac gag gag cca gtg aca cca gag ccg gaa gtg gaa ccg ccc agt gcc Asn Glu Glu Pro Val Thr Pro Glu Pro Glu Val Glu Pro Pro Ser Ala 10 15 20	281
ccc gag ctc aag caa ggg ctg tat gag ctc tca gca agc aac ttt gag Pro Glu Leu Lys Gln Gly Leu Tyr Glu Leu Ser Ala Ser Asn Phe Glu 25 30 35	329
ctg cac gtt gca caa ggc gac cac ttt atc aag ttc ttc gct ccg tgg Leu His Val Ala Gln Gly Asp His Phe Ile Lys Phe Phe Ala Pro Trp 40 45 50	377
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ctt ctc t Leu Leu :	tgg ttc Trp Phe 105	cga (	gat Asp	gly ggg	aaa Lys	aag Lys 110	gtg Val	gat Asp	cag Gln	tac Tyr	aag Lys 115	gga Gly	aag Lys	569
cgg gat (	ttg gag Leu Glu 120	tca Ser	ctg Leu	agg Arg	gag Glu 125	tac Tyr	gtg Val	gag Glu	tcg Ser	cag Gln 130	ctg Leu	cag Gln	cgc Arg	617
aca gag Thr Glu '	act gga Thr Gly	gcg Ala	acg Thr	gag Glu 140	acc Thr	gtc Val	acg Thr	ccc Pro	tca Ser 145	gag Glu	gcc Ala	ccg Pro	gtg Val	665
ctg gca ( Leu Ala ) 150	gct gag Ala Glu	Pro	gag Glu 155	gct Ala	gac Asp	aag Lys	ggc Gly	act Thr 160	gtg Val	ttg Leu	gca Ala	ctc Leu	act Thr 165	713
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gcc gaa Ala Glu 215	gta gad Val Asr	tgc Cys	act Thr	gct Ala 220	gaa Glu	cgg Arg	aat Asn	atc Ile	tgc Cys 225	agc Ser	aag Lys	tat Tyr	tcg Ser	905
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ctg agc Leu Ser		Lys					gaa	ca c	agtt	ggag	g tc	acct	ctcc	1053
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	-	_		_	aaa Lys 145		-				_			_		543
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		_			acc Thr				_	-	-		_			735
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130 135 140

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Met	Tyr	Leu	Gly 210	Gly	Leu	Pro	Glu	Asn 215	Arg	Ala	ggc Gly	Leu	11e 220	Leu	Pro		1213
Thr	Glu	Leu 225	Trp	Thr	Ala	Met	Leu 230	Asn	Tyr	Gly	tac Tyr	Val 235	Gly	Сув	Ile		1261
Arg	Asp 240	Leu	Phe	Ile	Asp	Gly 245	Arg	Ser	Lys	Asn	att Ile 250	Arg	Gln	Leu	Ala		1309
Glu 255	Met	Gln	Asn	Ala	Ala 260	Gly	Val	Lys	Ser	Ser 265	tgt Cys	Ser	Arg	Met	Ser 270		1357
Ala	Lys	Gln	Cys	Asp 275	Ser	Tyr	Pro	Cys	Lys 280	Asn	aat Asn	Ala	Val	Cys 285	Lys		1405
Asp	Gly	Trp	Asn 290	Arg	Phe	Ile	Cys	Asp 295	Cys	Thr	ggc	Thr	300	Tyr	Trp		1453
Gly	Arg	Thr 305	Cys	Glu	Arg	Glu	Ala 310	Ser	Ile	Leu	agc Ser	Tyr 315	Asp	Gly	Ser		1501
Met	Tyr 320	Met	Lys	Ile	Ile	Met 325	Pro	Met	Val	Met	cat His 330	Thr	Glu	Ala	Glu		1549
gat Asp 335	Val	Ser	ttc Phe	cgc	Phe	atg Met	tcc Ser	cag Gln	cga Arg	gct Ala 345	tat Tyr	Gly	ctg Leu	ctg Leu	gtg Val 350		1597
gct Ala	acg Thr	acc Thr	s tcc Ser	agg Arg 355	Asp	tct Ser	gcc	gac Asp	acc Thr 360	Leu	cgt Arg	ctg Leu	gag Glu	ctg Leu 365	Asp		1645
Gly	Gly	Arg	7 Val 370	Lys	Leu	Met	Val	Asn 375	. Leu	Asp	Cys	Ile	380	Ile	aac Asn		1693
tgt Cys	aac Asn	tcc Ser	ago Ser	aaa Lys	gga Gly	cca Pro	gag Glu	acc Thr	t t g Leu	tat Tyr	gca Ala	ggg Gly	Gln	aag Lys	ctc Leu		1741

385 390 395 .

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gag Glu	aaa Lys	cgc Arg	tac Tyr 450	atc Ile	tcc Ser	gtt Val	gtc Val	ccc Pro 455	tcc Ser	agc Ser	ttt Phe	att Ile	ggc Gly 460	cat His	ctg Leu	1933
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aag Lys	acc Thr	acc Thr	tca Ser 530	Pro	gat Asp	ggc Gly	ttc Phe	att Ile 535	Leu	ttc Phe	aat Asn	agt Ser	ggt Gly 540	Asp	ggc	2173
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Phe	Asp 560	Let	ı Gly	Asn	Gly	9ro 565	Asn	Val	Ile	Lys	570	Asn	Ser	: Asp	cgc Arg	2269
Pro 575	Leu	ı aat ı Asr	gac n Asp	aac Asr	cag Glr 580	Trp	cac His	aat Asn	gto Val	gto Val	. Ile	act Thr	cgg Arg	gac JAsp	aat Asn 590	2317
agt Ser	aac Asr	act Thi	cat r His	ago Ser 595	: Le	aaa Lys	gtg Val	g gac L Asp	t acc	Lys	gtg Val	gto Val	act Thr	Glr 605	gtt Val	2365
ato Ile	aat Asr	ggt Gly	t gcd y Ala 610	Lys	a aat s Asr	ctg Leu	gat 1 Asp	ttg Lev 615	Lys	ggt Gly	gat Asp	: cto Lev	tat Tyr 620	Met	gct : Ala	2413
ggt Gly	ct <u>c</u> / Le	g gcc 1 Ala 62!	a Glr	a ggo a Gly	e atg / Met	tac Tyr	e ago Sei 630	r Asr	cto Le	c cca	a aag o Lys	Let 635	ı Val	g gco L Ala	tct Ser	2461
cga Arg	a gat g Asp	gg Gl	c ttt y Phe	caq e Gl	g ggo n Gly	c tgt y Cys	cta Lei	a gca ı Ala	tca Sei	a ggg	g gad y Asp	tto Lev	g aat 1 Asi	t gga n Gly	a cgc / Arg	2509

640 645 650

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cgt Arg	ggc Gly	tgt Cys	gaa Glu	gga Gly 675	ccc Pro	agt Ser	acc Thr	acc Thr	tgc Cys 680	cag Gln	gaa Glu	gat Asp	tca Ser	tgt Cys 685	gcc Ala	2605
aac Asn	cag Gln	Gly aaa	gtc Val 690	tgc Cys	atg Met	caa Gln	caa Gln	tgg Trp 695	gag Glu	ggc Gly	ttc Phe	acc Thr	tgt Cys 700	gat Asp	tgt Cys	2653
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gtc Val	ttc Phe	aac Asn 785	att Ile	ggc Gly	aca Thr	gtt Val	gac Asp 790	atc Ile	tcc Ser	atc Ile	aaa Lys	gag Glu 795	gag Glu	aga Arg	acc Thr	2941
cct Pro	gta Val 800	aat Asn	gac Asp	ggc Gly	aaa Lys	tac Tyr 805	cat His	gtg Val	gta Val	cgc Arg	ttc Phe 810	acc Thr	agg Arg	aac Asn	ggc Gly	2989
ggc Gly 815	Asn	gcc Ala	acc Thr	ctg Leu	cag Gln 820	gtg Val	gac .Asp	aac Asn	tgg Trp	cca Pro 825	gtg Val	aat Asn	gaa Glu	cat His	tat Tyr 830	3037
cct Pro	aca Thr	ggc Gly	aac Asn	act Thr 835	gat Asp	aat Asn	gaa Glu	cgc Arg	ttc Phe 840	caa Gln	atg Met	gta Val	aaa Lys	cag Gln 845	aaa Lys	3085
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ggc Gly	cgg Arg	cag Gln 865	tta Leu	acc Thr	atc Ile	ttc Phe	aac Asn 870	act Thr	cag Gln	gcg Ala	caa Gln	ata Ile 875	gcc Ala	att Ile	ggt Gly	3181
		Asp		gga Gly												3229
				aaa Lys												3277

WO 01/55437			PCT/US01/02623
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ttg gga aca aca cag acg Leu Gly Thr Thr Gln Thr 930	acc tcc atg cca Thr Ser Met Pro 935	cca gaa atg tct act Pro Glu Met Ser Th 940	act 3373 Thr
gtc atg gaa acc act act Val Met Glu Thr Thr Thr 945	aca atg gcg act Thr Met Ala Thr 950	acc aca acc cgt aa Thr Thr Thr Arg Ly 955	g aat 3421 s Asn
cgc tct aca gcc agc att Arg Ser Thr Ala Ser Ile 960	cag cca aca tca Gln Pro Thr Ser 965	gat gat ctt gtt tc Asp Asp Leu Val Se 970	a tct 3469 r Ser
gct gaa tgt tca agt gat Ala Glu Cys Ser Ser Asp 975 980	Asp Glu Asp Phe	gtt gaa tgt gag cc Val Glu Cys Glu Pr 985	g agt 3517 o Ser 990
aca gca aac ccc acg gag Thr Ala Asn Pro Thr Glu 995	ccg gga atc aga Pro Gly Ile Arg 1000	Arg Val Pro Gly Al	a Ser
gag gtg atc cgg gag tcg Glu Val Ile Arg Glu Ser 1010	agc agc aca aca Ser Ser Thr Thr 1015	ggg atg gtc gtc gg Gly Met Val Val Gl 1020	c att 3613 y Ile
gtg gct gct gcc gcc ctc Val Ala Ala Ala Ala Leu 1025	tgc atc ttg atc Cys Ile Leu Ile 1030	ecto otg tao god at Leu Leu Tyr Ala Me 1035	g tac 3661 et Tyr
aag tac agg aac agg gad Lys Tyr Arg Asn Arg Asg 1040	gag ggg toc tat Glu Gly Ser Tyr 1045	caa gtg gac gag ac Gln Val Asp Glu Ti 1050	eg egg 3709 nr Arg
aac tac atc agc aac tcc Asn Tyr Ile Ser Asn Ser 1055 1060	r Ala Gln Ser Ası	e ggc acg ctc atg as n Gly Thr Leu Met Ly 1065	ag gag 3757 ys Glu 1070
aag cag cag agc tcg aag Lys Gln Gln Ser Ser Lys 1075	g agc ggc cac aag s Ser Gly His Ly: 108	E Lys Gin Lys Asn L	ys Asp
agg gag tat tac gtg ta Arg Glu Tyr Tyr Val  * 1090	a acatgc gaacact	get cacaegegag tttt	cacagt 3859
tatttctatc cacgcctatg	aatetttgga eggtg	agatc tcacagatgt ca	gaactgct 3919
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cgctctggag ccggacggtg			
aggacctttt actaaaaggt			
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gca Ala	ttg Leu	agc Ser 35	tac Tyr	gtg Val	tct Ser	gaa Glu	att Ile 40	gly aaa	aaa Lys	gcc Ala	cct Pro	ctc Leu 45	cag Gln	cgg Arg	gcc Ala	261
ctg Leu	cag Gln 50	gtc Val	act Thr	gtc Val	cct Pro	cat His 55	ttc Phe	ctg Leu	gac Asp	tgg Trp	agt Ser 60	gga Gly	gag Glu	gcg Ala	ctt Leu	309
cag Gln 65	ccc Pro	acc Thr	agg Arg	atc Ile	cgg Arg 70	att Ile	ctg Leu	aat Asn	gtc Val	cat His 75	gtg Val	ccc Pro	cgc	ctc Leu	cac His 80	357
ctg Leu	aaa Lys	ttc Phe	att Ile	gct Ala 85	ggt Gly	ttc Phe	gga Gly	gtg Val	cgc Arg 90	ctg Leu	ctg Leu	gca Ala	gca Ala	gct Ala 95	aat Asn	405
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cct Pro	gtg Val	gaa Glu 115	ctg Leu	ctg Leu	gct Ala	gac Asp	acc Thr 120	Arg	gtg Val	acc Thr	cag Gln	agc Ser 125	tcc Ser	atc Ile	agg Arg	501
acc Thr	cct Pro 130	gtg Val	gtc Val	agc Ser	atc Ile	tct Ser 135	Ala	tgc Cys	tct Ser	tta Leu	ttc Phe 140	Ser	ggc	cac His	gcc Ala	549
aac Asn 145	Glu	ttt Phe	gat Asp	ggc	agt Ser 150	Asn	ago Ser	acc Thr	tcc Ser	cac His	Ala	ctg Leu	ctg Leu	gtc Val	Leu 160	597
gtg Val	cag Gln	aag Lys	g cac s His	att Ile 165	Lys	gct Ala	gto Val	ttg Leu	agt Ser 170	Asn	aag Lys	ctg Leu	tgo Cys	Lev 175	agc Ser	645
ato Ile	tcc Ser	aac Asr	cto Lev 180	val	cag Gln	ggt Gly	gto Val	aat Asn 185	Val	cac His	ctg Lev	ggc Gly	acc Thr 190	Let	att Ile	693
Gly	cto Leu	aac Ası 199	n Pro	gtg Val	ggt Gly	cct Pro	gag Glu 200	ı Ser	caç Glr	ato lle	cgc Arg	tat Tyr 205	Ser	ato Met	g gtc : Val	741
agt Ser	gtg Val	Pro	e act	gto Val	acc Thr	e agt Ser 215	: Asp	tac Tyr	att	tco Ser	cto Lev 220	ı Glı	gto Val	aat Asr	gct Ala	789
	Leu					/ Lys					ı Pro				acc Thr 240	837
					Arg					c Glu					c acc a Thr	885
gtg	ggg	ct	c tc	cas	g cag	gctg	g tt	t gad	e to	t gcg	gcto	c ctg	get	gct	g cag	933

PCT/US01/02623 WO 01/55437 Val Gly Leu Ser Gln Gln Leu Phe Asp Ser Ala Leu Leu Leu Gln 265 981 aag gcc ggt gcc ctc aac ctg gac atc aca ggg cag ctg agg tcg gat Lys Ala Gly Ala Leu Asn Leu Asp Ile Thr Gly Gln Leu Arg Ser Asp 1029 gac aac ctg ctg aac acc tct gct ctg ggc cgg ctc atc ccg gag gtg Asp Asn Leu Leu Asn Thr Ser Ala Leu Gly Arg Leu Ile Pro Glu Val 290 1077 gcc cgc cag ttt ccc gag ccc atg cct gtg gtg ctc aag gtg cgg ctg Ala Arg Gln Phe Pro Glu Pro Met Pro Val Val Leu Lys Val Arg Leu 305 310 ggt gcc aca cct gtg gcc atg ctc cac aca aac aac gcc acc ctg cgg 1125 Gly Ala Thr Pro Val Ala Met Leu His Thr Asn Asn Ala Thr Leu Arg 330 325 ctg cag ccc ttc gtg gag gtc ctg gcc aca gcc tcc aac tcg gct ttc 1173 Leu Gln Pro Phe Val Glu Val Leu Ala Thr Ala Ser Asn Ser Ala Phe 345 cag tcc ctc ttc tcc ctg gat gtg gta gtg.aac ttg aga ctc cag ctc 1221 Gln Ser Leu Phe Ser Leu Asp Val Val Val Asn Leu Arg Leu Gln Leu 360 1269 tet gtg tee aag gtg aag ett eag ggg ace acg tet gtg etg ggg gat Ser Val Ser Lys Val Lys Leu Gln Gly Thr Thr Ser Val Leu Gly Asp 375 gtc cag ctc acg gtg gcc tcc tcc aac gtg ggc ttc att gat aca gat 1317 Val Gln Leu Thr Val Ala Ser Ser Asn Val Gly Phe Ile Asp Thr Asp 390 395 cag gtg cgc aca ctg atg ggc acc gtt ttt gag aag ccc ctg ctg gac 1365 Gln Val Arg Thr Leu Met Gly Thr Val Phe Glu Lys Pro Leu Leu Asp 405 1413 cat etc aat get etc ttg gec atg gga att gec etc eet ggt gtg gte His Leu Asn Ala Leu Leu Ala Met Gly Ile Ala Leu Pro Gly Val Val 1461 aac etc cae tat gtt gee eet gag ate ttt gte tat gag gge tae gtg Asn Leu His Tyr Val Ala Pro Glu Ile Phe Val Tyr Glu Gly Tyr Val 440 gtg ata tee agt gga ete tte tae eag age tga ggeaagae eactgggagg 1512 Val Ile Ser Ser Gly Leu Phe Tyr Gln Ser \* cctgagagtg ggccagctcg ctgctcaggc gaatttctca tttcaagcca ctggggaaac 1572 tgaggcaaaa ccatacttag tcatcaccaa caagctggac tgcttagctg ggctgtttta 1632 tettecetga gtgcctgggt etecetecet caettetgee etttecette etecteetet 1692 totoctccct cttccctcat ctcccccctc cttcctctgc cccaccccag gggggagcag 1752 actgetecte caggetgtat agacetgece tettgeatta aacaaettet ettgagetge 1812

1822

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gatatggetg gaaggacata gagtaaatga teggtetggt teategetaa aggagaetta	180
ggaacctag atg aag ttg gta ctt ctg aga aag aca tct ctt tct gtt  Met Lys Leu Val Leu Leu Arg Lys Thr Ser Leu Ser Val  1 5 10	228
ttc act act cta ttc tca gta tcc agt tct cag tac cca gtt ctc agt Phe Thr Thr Leu Phe Ser Val Ser Ser Ser Gln Tyr Pro Val Leu Ser 15 20 25	276
acc tot att tgt aat act oot gta ttt agt act ttg ttt tta gtg toc Thr Ser Ile Cys Asn Thr Pro Val Phe Ser Thr Leu Phe Leu Val Ser 30 35 40 45	324
tgt tct gtt aac cct ctt cct agt acc gta ttt tta gta ctg cta tac Cys Ser Val Asn Pro Leu Pro Ser Thr Val Phe Leu Val Leu Leu Tyr 50 55 60	372
tca gtt gcc tgt ctg tag tacccc tgtacgtagt actcttttct tacaactctg Ser Val Ala Cys Leu * 65	426
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gac ctg aag gac acc tat gcc tcc ctg ggc aag acc aac gtc aag gac Asp Leu Lys Asp Thr Tyr Ala Ser Leu Gly Lys Thr Asn Val Lys Asp 55 60 65	667
gac gag ctg gac gcc atg ctc aaa gag gcc tcg ggg ccc atc aac ttc Asp Glu Leu Asp Ala Met Leu Lys Glu Ala Ser Gly Pro Ile Asn Phe 70 75 80 85	715
acc atg ttt ctg aac ctg ttt ggg gag aag ctg agc ggt acc gac gcc Thr Met Phe Leu Asn Leu Phe Gly Glu Lys Leu Ser Gly Thr Asp Ala 90 95 100	763
gag gag acc att ctt aac gcc ttc aag atg ctg gac ccg gac ggg aaa Glu Glu Thr Ile Leu Asn Ala Phe Lys Met Leu Asp Pro Asp Gly Lys 105 110 115	811
ggg aaa atc aac aag gag tac atc aag cgt ctg ctg atg tcc cag gct Gly Lys Ile Asn Lys Glu Tyr Ile Lys Arg Leu Leu Met Ser Gln Ala 120 125 130	859
gac aag atg acg gcg gaa gag gtg gac cag atg ttc cag ttc gcc tcc Asp Lys Met Thr Ala Glu Glu Val Asp Gln Met Phe Gln Phe Ala Ser 135 140 145	907
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gca gcc tcg gcc tcg ggt cag gcg gaa ggt aaa aag atc acc gat Ala Ala Ser Ala Ala Ser Gly Gln Ala Glu Gly Lys Lys Ile Thr Asp 10 15 20	160												
ctg cgg gtc atc gat ctg aag tcc gag ctg aag cgg cgg aac tta gac Leu Arg Val Ile Asp Leu Lys Ser Glu Leu Lys Arg Arg Asn Leu Asp 25 30 35 40	208												
atc acc gga gtc aag acc gtg ctc atc tcc cga ctc aag cag gct att Ile Thr Gly Val Lys Thr Val Leu Ile Ser Arg Leu Lys Gln Ala Ile 45 50 55	256												
gaa gag gaa gga ggc gat cca gat aat att gaa tta act gtt tca act Glu Glu Glu Gly Gly Asp Pro Asp Asn Ile Glu Leu Thr Val Ser Thr 60 65 70	304												
gat act cca aac aag aaa cca act aaa ggc aaa ggt aaa aaa cat gaa Asp Thr Pro Asn Lys Lys Pro Thr Lys Gly Lys Gly Lys Lys His Glu 75 80 85	352												
gca gat gag ttg agt gga gat gct tct gtg gaa gat gat gct ttt atc Ala Asp Glu Leu Ser Gly Asp Ala Ser Val Glu Asp Asp Ala Phe Ile 90 95 100	400												
aag gac tgt gaa ttg gag aat caa gag gca cat gag caa gat gga aat Lys Asp Cys Glu Leu Glu Asn Gln Glu Ala His Glu Gln Asp Gly Asn 105 110 115	448												
gat gaa cta aag gac tct gaa gaa ttt ggt gaa aat gaa gaa aat Asp Glu Leu Lys Asp Ser Glu Glu Phe Gly Glu Asn Glu Glu Asn 125 130 135	496												
gtg cat tcc aag gag tta ctc tct gca gaa gaa aac aag aga gct cat Val His Ser Lys Glu Leu Leu Ser Ala Glu Glu Asn Lys Arg Ala His 140 145 150	544												
gaa tta ata gag gca gaa gga ata gaa gat ata gaa aaa gag gac atc Glu Leu Ile Glu Ala Glu Gly Ile Glu Asp Ile Glu Lys Glu Asp Ile 155 160 165	592												
gaa agt cag gaa att gaa gct caa gaa ggt gaa gat gat acc ttt cta Glu Ser Gln Glu Ile Glu Ala Gln Glu Gly Glu Asp Asp Thr Phe Leu 170 175 180	640												
aca gcc caa gat ggt gag gaa gaa gaa aat gag aaa gaa g	688												
gct gag gct gat cac aca gct cat gaa gag atg gaa gct cat acg act Ala Glu Ala Asp His Thr Ala His Glu Glu Met Glu Ala His Thr Thr 205 210 215	736												
gtg aaa gaa gct gag gat gac aac atc tcg gtc aca atc cag gct gaa Val Lys Glu Ala Glu Asp Asp Asn Ile Ser Val Thr Ile Gln Ala Glu 220 225 230	784												
gat gcc atc act ctg gat ttt gat ggt gat gac ctc cta gaa aca ggt	832												

PCT/US01/02623 WO 01/55437 Asp Ala Ile Thr Leu Asp Phe Asp Gly Asp Asp Leu Leu Glu Thr Gly 240 aaa aat gtg aaa att aca gat tgt gaa gca agt aag cca aaa gat ggg 880 Lys Asn Val Lys Ile Thr Asp Cys Glu Ala Ser Lys Pro Lys Asp Gly 255 250 cag ggc gcc att gca cag agg ccg gat aag gaa agc aag gat tat gag 928 Gln Gly Ala Ile Ala Gln Arg Pro Asp Lys Glu Ser Lys Asp Tyr Glu 275 265 270 atg aat gcg agc cat aaa gat ggt aag aag gaa gac tgc gtg aag ggt 976 Met Asn Ala Ser His Lys Asp Gly Lys Lys Glu Asp Cys Val Lys Gly gac cet gte gag aag gaa gee aga gaa agt tet aag aaa gea gaa tet 1024 Asp Pro Val Glu Lys Glu Ala Arg Glu Ser Ser Lys Lys Ala Glu Ser 305 300 1076 gga gac caa aga aaa gga tta ctt tga agaaa gggccctcgt ctactggggc Gly Asp Gln Arg Lys Gly Leu Leu 315 ctctggtcaa gcaaagagct cttcaaagga atctaaagac agcaagacat catctaaaga 1136 1196 tgacaaagga agtacaagta gtactagtgg tagcagtgga agctcaacta aaaatatctg ggttagtgga ctttcatcta ataccaaagc tgctgatttg aagaacctct ttggcaaata 1256 1316 tggaaaggtt ctgagtgcaa aagtagttac aaatgctcga agtcctgggg caaaatgcta tggcattgta actatgtett caageacaga ggtgtecagg tgtattgeae atetteateg 1376 cactgagetg catggacage tgatttetgt tgaaaaagta aaaggtgate cetetaagaa 1436 agaaatgaag aaagaaaatg atgaaaagag tagttcaaga agttctggag ataaaaaaaa 1496 tacgagtgat agaagtagca agacacaagc ctctgtcaaa aaagaagaga aaagatcgtc 1556 tgagaaatct gaaaaaaag aaagcaagga tactaagaaa atagaaggta aagatgagaa 1616 1656 gaatgataat ggagcaagtg gccaaacatc agaatcgatt

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ggg tat ctc tgc ttc tgt gcc ctt cag tgg act gag cta gga aat gta Gly Tyr Leu Cys Phe Cys Ala Leu Gln Trp Thr Glu Leu Gly Asn Val 10 15 20	283
tgt gtg tgt gca cac ata tgc cgt tgc aca cac atg cag gtt tca ggg Cys Val Cys Ala His Ile Cys Arg Cys Thr His Met Gln Val Ser Gly 25 30 35	331
atc aca agt ccg gtc cat gtc cac atc cat agg gtt ctt tct tgc ctt Ile Thr Ser Pro Val His Val His Ile His Arg Val Leu Ser Cys Leu 40 45 50	379
atc cat ttc acc tct tag agcaga ggactttcac catttctatt gaacatgagt Ile His Phe Thr Ser * 55	433
ataatatgta gtccttacct aagaggattc tgtggatctt ctctggggtt ctcaggggcc	493
atggaacatg tcagagcaaa tgttggaatg gattacccag aatgtgagta gtgtgagtgg	553
ggcactgttg gactcagtcc caacccccta acgcgagttt gcatgaaaaa ttcatatctt	613
acttagggcc atcctaactt tcttgcttcc caaagggagg gtagatcaaa acataaggga	673
aaggaggggt cataaacttg ttttgaaggt acccggggga accctaaaca ttataggggt	: 733
ctagtctatg geogactagt egegactata aacgaageet teatcatagg gaaaaaggtg	<del>j</del> 793
caggactttc ttacacatgg ctagtagaac gggtctaggc tagcatgaga ccttccatgc	853
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Arg Cys His Pro Ala Arg Ala Ser Arg Glu Arg Pro Ser Glu Asp Asn
30 35 40

ttg tca cca gcc gtc aaa gaa gag agt ggc ttt gtg gtc tct gaa cat 316

1																		
	beu	Ser 45	Pro	Ala	Val	Lys	Glu 50	Glu	Ser	Gly	Phe	Val 55	Val	Ser	Glu	His		
				ctg Leu			Lys						taa *	ttg	tgat	gaa	365	
į	ataa	ttt	aaa	ccat	cagga	aa t	aaat	gaggo	tg	ttaa	gcta	agti	cag	att	ccat	ttgc	ca 425	
	tgca	cat	gtg	tcta	gcag	cc t	gtgt	gcagi	t ta	aaag	aaat	tgaa	atta	tat	tagc	tcat	ga 485	
•	gtag	gaag	tga	aaca	gata	ct g	taaa	tgaaa	a ca	agtt	gctg	tata	agcg	atg	acat	cgtg	tt 545	
9	gaac	ccat	ttc	acag	agtt	ac a	gttt	gtate	g at	cact	gtat	caa	aagt	ggt	atat	tatt	ta 605	
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	atgg	ggta	ggt	agag	agga	tg t	gagc	tgga	t gg	gcag	aaca	aaa	caat	cca	cagg	ttac	gg 725	
	gcct	ttga	agg	gagt	ggga	aa a	aaat	cacg	c gt	catt	ggag	ccc	agtt	gcc	ctgt	taga	gc 785	i
	ccga	aacg	gag	tcca	catc	ac g	ccgc	ctgc	a ct	tggg	cata	cgc	gatc	acg	ggaa	cgct	cc 845	į
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		<2	11>	1113														
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acc ttg tcc act ctg aca gtg acc agt gcc cat cct gaa gac agc agc Thr Leu Ser Thr Leu Thr Val Thr Ser Ala His Pro Glu Asp Ser Ser

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wo	01/5	5437												1	PCT/US	01/02623
90					95					100					105	
			tgc Cys	_	-	_		_	-	_		_	_	_		386
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ttc Phe	cca Pro	ccc Pro 140	gag Glu	gtc Val	gct Ala	gtg Val	ttt Phe 145	gag Glu	cca Pro	tca Ser	gaa Glu	gca Ala 150	gag Glu	atc Ile	tcc Ser	482
			aag Lys													530
			gag Glu													578
			aca Thr													626
			tac Tyr 205													674
	_		ccc Pro	_				_	_		_	_				722
			aat Asn													770
_		_	agc Ser	-		-			_	_	_	_				818
			tac Tyr													866
			999 Gly 285													914
			gcc Ala											ctc	caaa	963
acca	atcco	ag ç	gtcat	tct	c at	tcct	cacco	c agg	gatto	ctcc	tgta	acct	gat (	ccca	atctgt	1023
gtto	cctaa	aa g	gtgat	tete	ca ct	tctg	cttc	cat	ctc	ctac	ttad	catga	aat a	actto	ctctct	1083
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435 495 aattatccag gtgtggtggc gggtgcttgt actgccagct acttgggagg ctgaggcagg 555 agaatggcgt gaacccagga ggcggagctt gcagtgagcc gagatcccac cactggactc cattetggcg aaagagcaga gactegteec aaaaaaaaga aaaaaaaggt tgtttttgag 675 gggccggcgg tttttccttt tggggggtaa aattattggg cctggqcgqg gtttaaaacq gggggggaa aaaacngntt ttcccnaaaa aa 767

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tctattcttt gttgat
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                     Met Glu Lys Tyr Phe His Thr Val Met Ile Lys
                                        5
                                                           10
```

ttg t Leu (	tgc Cys	cat His	caa Gln 15	ctt Leu	tat Tyr	aac Asn	gta Val	Tyr 20	gtg Val	tgc Cys	Phe	Phe	Cat His 25	tta Leu	Ile	157
gtt t Val I	ttg Leu	gga Gly 30	gat Asp	att Ile	gct Ala	ata Ile	gac Asp 35	tac Tyr	att Ile	att Ile	gtt Val	ccc Pro 40	aat Asn	att Ile	tcc Ser	205
tac ( Tyr 1	ctc Leu 45	tct Ser	ata Ile	tct Ser	ata Ile	ccc Pro 50	ttt Phe	gta Val	gtt Val	act Thr	aac Asn 55	att Ile	aga Arg	ggt Gly	aga Arg	253
gat a Asp : 60	att Ile	ttc Phe	cac His	ccc Pro	tgt Cys 65	aat Asn	gtg Val	gcc Ala	ttg Leu	gtc Val 70	atg Met	tga *	ctt	ggaai	tgt	302
tagt	agtt	cct (	gatgi	tgcad	ca g	aggc	tgta	c at	ggac	tttc	agc	attg	ggt	ttac	tctctc	362
gggt	ttct	tgc	tgtt	tccat	ta c	aaaga	aatgi	t ac	cctg	ggtg	gcc	cacca	agc	cact	gagata	422
tgtg	aato	cca .	actt	gaact	tc a	actc	atgg	c ct	ggag	ccaa	gtt	ccac	cag	tcct	aactag	482
ctta	gcc	aaa .	atcc	agct	ga t	ctga	aagt	д са	tgaa	tgag	aaa	taaa	agc	ttat	tatttt	542
tttt	anna	ann	aann	annn	aa a	aaaa	aaag	a ct	tttt	ttta	<b>a</b> aa	gggg	<b>aa</b> a	gggt	tttctc	602
cttt	tcg	agg	aaaa	aaat	ta a	taaa	atga	g tg	gcgc	cccc	ctc	ttcc	ctt	gcgc	gagggg	662
gtaa	aag	gcc	cggn	nnnn	nn c	cggc	cccc	c cc	ccgc	cccc	ccc	cccc	ggc	ggaa	agccgc	722
aaaa	ıggn	aaa	aaaa	ggng	gg g	ngaa	gtgg	g gt	gtcc	cccc	ccc	cacc	ccc	cccc	ccacta	a 782
at																784

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<211> 597

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (314)..(463)

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15 20 25	
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aag tot ata att tto taa acotaa ototgatgoa gtootactoo Lys Ser Ile Ile Phe * 45 50	taatatttac 499
aaggcctaga acaagagtat ataaatggca gcccacattc tacgggtc	ta aatatataca 559
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ggtaaaatct gctccgacca gagagaaaaa actaattcat at atg	aat ata gta 174 Asn Ile Val
ttt gta atc ctc ttg ttt aaa gac atg caa gtt cta gaa Phe Val Ile Leu Leu Phe Lys Asp Met Gln Val Leu Glu 5 15	gta ttt gta 222 Val Phe Val 20
ctg ctt aat gtt tta aca act cta aca ata ata gca gcg Leu Leu Asn Val Leu Thr Thr Leu Thr Ile Ile Ala Ala 25 30	ggc ata ctt 270 Gly Ile Leu 35
tgt acc agt ttt tgc tgt aag cct ttt ata tat att aat Cys Thr Ser Phe Cys Cys Lys Pro Phe Ile Tyr Ile Asn 40 45	cct ctt taa 318 Pro Leu * 50
aaccacccta tcaagtacaa gataataatt tgatatggtt gatgaagc	aa ctgatgggaa 378
aaaagagagg ttaaataatt tgccccaaat cttattaagt gatgtagc	ca gcatctgaac 438
ccaatcagac tgtagactag agcctcetec caaccactca getttget	gc ttcccacata 498
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Met Thr Asn Phe Phe His Leu Leu Pro Leu Leu Pro Ser Leu
1 5 10 15

ttt tcc ccc tcc tca aaa acg cat agc ttc aat att cat aag atc atc Phe Ser Pro Ser Ser Lys Thr His Ser Phe Asn Ile His Lys Ile Ile 20 25 30	155
atc atc atc ctt ttc ttc aac agc att ttc ttg tat cct aga gat tac  Ile Ile Ile Leu Phe Phe Asn Ser Ile Phe Leu Tyr Pro Arg Asp Tyr  35 40 45	203
ctt aaa ata agg aat tgg cta caa agt aat acc ttg gaa aga gaa ata Leu Lys Ile Arg Asn Trp Leu Gln Ser Asn Thr Leu Glu Arg Glu Ile 50 55 60	251
gaa tgg atc acc tct ata agg tgc tta tgt aac tct gga act acg ttt Glu Trp Ile Thr Ser Ile Arg Cys Leu Cys Asn Ser Gly Thr Thr Phe 65 70 75	299
ata ttt cca tta acc aca aag tcc aca tga g tcatacttat ttttctgtct Ile Phe Pro Leu Thr Thr Lys Ser Thr * 80 85	350
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aatctgtacc gggaggtg atg ctg gag aac tat ggg aac ct Met Leu Glu Asn Tyr Gly Asn Le 1 5	g gtc tca gtg 1011 u Val Ser Val 10
gga tgt cag ctt tcc aaa cct ggc gtg att tcc cag ttg Gly Cys Gln Leu Ser Lys Pro Gly Val Ile Ser Gln Leu 15	Glu Lys Gly 25
gaa gaa cca tgg ctg atg gag aga gat att tca gga gtt Glu Glu Pro Trp Leu Met Glu Arg Asp Ile Ser Gly Val 30 35 40	Pro Ser Ser
gac ttg aag agc aaa aca aaa acc aaa gag tca gcc tta Asp Leu Lys Ser Lys Thr Lys Thr Lys Glu Ser Ala Leu 45 50 55	Gln Asn Asp
att tcg tgg gaa gaa cta cat tgt ggc cta atg atg gaa Ile Ser Trp Glu Glu Leu His Cys Gly Leu Met Met Glu 60 65 70	Arg Phe Thr 75
aaa gga agc agc atg tat tcc acc ttg gga aga atc tcc Lys Gly Ser Ser Met Tyr Ser Thr Leu Gly Arg Ile Ser 80 . 85	: Lys Cys Asn 90
aag cta gaa agc caa caa gag aac caa aga atg ggt aag Lys Leu Glu Ser Gln Gln Glu Asn Gln Arg Met Gly Lys 95 100	: Gly Gln Ile 105
ccc ctg atg tgc aag aaa aca ttc act cag gag aga ggc Pro Leu Met Cys Lys Lys Thr Phe Thr Gln Glu Arg Gly 110 115	y Gln Glu Ser )
aat aga ttt gag aaa aga att aat gtg aag tca gaa gtt Asn Arg Phe Glu Lys Arg Ile Asn Val Lys Ser Glu Val 125 130 135	l Met Pro Gly
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aca aaa atg aaa acc ttt gag tgt aat att tgt gaa aaa Thr Lys Met Lys Thr Phe Glu Cys Asn Ile Cys Glu Lys 175 180	a atc ttc aaa 1539 s Ile Phe Lys 185
cag ctt att cac ctt act gaa cac atg aga att cat acc Gln Leu Ile His Leu Thr Glu His Met Arg Ile His Th 190 195 200	r Gly Glu Lys
cct ttc aga tgt aag gaa tgt gga aaa gcc ttt agc caa Pro Phe Arg Cys Lys Glu Cys Gly Lys Ala Phe Ser Gla 205 210	
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gtt (	aga Arg	att Ile	cat His 255	acc Thr	GJA aaa	gaa Glu	aag Lys	ccc Pro 260	tat Tyr	gaa Glu	tgt Cys	agg Arg	gta Val 265	tgt Cys	gag Glu	1779
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gtt Val	aga Arg 285	gag Glu	aaa Lys	cct Pro	ttt Phe	aca Thr 290	tgc Cys	aaa Lys	gac Asp	tgt Cys	gga Gly 295	aaa Lys	gcg Ala	ttt Phe	ttc Phe	1875
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aaa Lys 380																2163
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ttc Phe	_		_		-	aata	ata (	ctaaa	acato	ca aa	agaat	tcta	t gt	tgga	gcac	2313
aaga	ttct	caa a	atcag	gtgg	tt c	cctg	atcc	c tca	aaaa	atcc	atti	tgtt	ttt q	ggati	tccaa	2373
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Met Leu Phe Thr Ser Phe Val Tyr Gly Leu att ttt att ttg ttt gat ttt tat ttt cta tca ttt gtt gaa agg gat 218 Ile Phe Ile Leu Phe Asp Phe Tyr Phe Leu Ser Phe Val Glu Arg Asp 15 gtt aaa atc ttc aac tgt aat ggt gaa ata gta ttg ttt cca ttt aat 266 Val Lys Ile Phe Asn Cys Asn Gly Glu Ile Val Leu Phe Pro Phe Asn 30 35 tct gtt cat ttt tgc ctg ata tgt ctt tat ata cac att taa gattatg 315 Ser Val His Phe Cys Leu Ile Cys Leu Tyr Ile His Ile \* 45 50 tetteetgat gagttgtgaa ttagaacatt atgaaatgtt atteteeggg aatattatte 375 teteettaca gtetatttta eteaatattg atatageaac teeateettt atataettae 435 tqtttacatg gtqtqccttt tcagaagcat ttaqtttcaa ttataqataq catataqatq 495 agacttgttt ttttttaaat ctattctgaa aatttctgat tttattatta ggaatattta 555 ggggaaatgt ttaataaatt aatattttgg gtttttcttt ctgccatttt tcatatttat ccctcctcct cccccaggaa aaattcaaaa ctctttctt caaactagta cgaaggataa 675 aaatacgctt ccccaccact cgtgggctcc tctctcatcg tcaccctttc ttacaactct 735

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795

855

915

975

1035

1069

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1 5

agc tcc cta act tta gtt ttt gcc tgg aat tac cca tta cat ttg atg
Ser Ser Leu Thr Leu Val Phe Ala Trp Asn Tyr Pro Leu His Leu Met
10 15 20

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aaaacttc atg tgt tta att ctg gtt atc tgg aaa att cac tat gca gaa Met Cys Leu Ile Leu Val Ile Trp Lys Ile His Tyr Ala Glu 1 5 10	170
ctt ata atg tta aat aaa cga gtt gtt aat aaa tgt aga tca tgt ctt Leu Ile Met Leu Asn Lys Arg Val Val Asn Lys Cys Arg Ser Cys Leu 15 20 25 30	218
atc caa aaa tgc cta tct aca tgt cat agt aca gtc att gtt tta tat Ile Gln Lys Cys Leu Ser Thr Cys His Ser Thr Val Ile Val Leu Tyr 35 40 45	266
caa tgc aga gag gaa gaa gct gtg atg tta ata aag ttg aat ttt aaa Gln Cys Arg Glu Glu Glu Ala Val Met Leu Ile Lys Leu Asn Phe Lys 50 55 60	314
atg aaa atc caa aga act ata tgt ata tag g ccaaataaaa agttacttga Met Lys Ile Gln Arg Thr Ile Cys Ile * 65 70	365
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cat ttc ccc att tcc att tat gac aac att ggt cat tgg cct cag tca His Phe Pro Ile Ser Ile Tyr Asp Asn Ile Gly His Trp Pro Gln Ser 30 35 40	206
ccg aaa gtc agg agg aag gaa gga aat gaa tat tta ttg aac ccc aat Pro Lys Val Arg Arg Lys Glu Gly Asn Glu Tyr Leu Leu Asn Pro Asn 45 50 60	254
atg tgc cag acc ctg gat tta aca ctt tta ggg ata gga gat tat tta Met Cys Gln Thr Leu Asp Leu Thr Leu Leu Gly Ile Gly Asp Tyr Leu 65 70 75	302
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gaggttetge aaagteaatt gaetttgeet ggtaagagge aaaaceagea teetttattt 415
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ctg atg att taa aca tagagttttt geetgtatet etececetaa gtetaggett 526
Leu Met Ile \*
90

ttt tet tet ete age aet tte eet ggg tgg ttg ett ate ate tge aea Phe Ser Ser Leu Ser Thr Phe Pro Gly Trp Leu Leu Ile Ile Cys Thr 471

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<212> DNA

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aactgtgaac atctgatctt gatactggct t atg ttg tct ctt gtt aag ctt 232 Met Leu Ser Leu Val Lys Leu 1

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ata cag gta gga tta tta cca agt gcc tac cgt gta cca gga ata gtt 328 Ile Gln Val Gly Leu Leu Pro Ser Ala Tyr Arg Val Pro Gly Ile Val

cta agc ctt gag aat aca gca cta ata agg cag act ccc tgc tca aat 376 Leu Ser Leu Glu Asn Thr Ala Leu Ile Arg Gln Thr Pro Cys Ser Asn

aga gcc aac taa tga aaaatcgata aaatagagac taaagagaga tccttagttg 431 Arg Ala Asn \*

491

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aaaaatctgg ttgtcctccg taacacctgc gataagacga tcgacggtag gtctatatcg 671

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<212> DNA

<213> Homo sapiens

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Met Arg Pro Leu Ala Gly Ala Pro Val

					t Arg	g Pro	Leu	ı Ala		/ Ala	i Pro	) Val	
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tat gcc Tyr Ala	tac a Tyr A	gg tta irg Leu 30	ctc ag Leu Se	e gga r Gly	ggt Gly	ggc Gly 35	aga Arg	agc Ser	aag Lys	tac Tyr	gcc Ala 40	aaa Lys	266
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gcc aga Ala Arg	gga a Gly I 60	ta aac le Asn	att gc Ile Al	c att a Ile 65	gtc Val	aac Asn	tat Tyr	gta Val	act Thr 70	Gly ggg	aat Asn	gtg Val	362
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gtg acc	tat g	Jac gac Asp Asp 110	gga ag Gly Se	c aca r Thr	aga Arg	ctg Leu 115	aat Asn	aac Asn	gat Asp	gcc Ala	aag Lys 120	aat Asn	506
gcc ata Ala Ile	Glu A	gca ctt Ala Leu 125	gga ag Gly Se	t aaa r Lys	gaa Glu 130	atc Ile	agg Arg	aac Asn	atg Met	aaa Lys 135	ttc Phe	agg Arg	554
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	Arg G	jaa aag Slu Lys		n His									650
		ect gca Pro Ala											698
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120 115 125 ctc ttt gaa aag gag att ctc aaa agg gac gtc gca cac aaa gtg ttt 968 Leu Phe Glu Lys Glu Ile Leu Lys Arg Asp Val Ala His Lys Val Phe gee aca act tog ata aag age tte tte ege cag eta aac ttg tat gge 1016 Ala Thr Thr Ser Ile Lys Ser Phe Phe Arg Gln Leu Asn Leu Tyr Gly 150 155 ttc cga aaa cgg cgt caa tgc act ttc agg acc ttc acc cgc att ttc 1064 Phe Arg Lys Arg Arg Gln Cys Thr Phe Arg Thr Phe Thr Arg Ile Phe 170 tcc gca aaa agg ctg gtc tcc atc ttg aat aag tta gag ttc tac tgc 1112 Ser Ala Lys Arg Leu Val Ser Ile Leu Asn Lys Leu Glu Phe Tyr Cys 180 185 cat cet tac ttt caa aga gac tee cet cac ete ete gtg agg atg aag 1160 His Pro Tyr Phe Gln Arg Asp Ser Pro His Leu Leu Val Arg Met Lys 200 195 aga aga gtg ggt gtc aag tct gca cca aga cat cag gag gag gac aag 1208 Arg Arg Val Gly Val Lys Ser Ala Pro Arg His Gln Glu Glu Asp Lys 210 215 cca gaa gct gct gga tcc tgt ctg gca cca gca gac act gag caa caa 1256 Pro Glu Ala Ala Gly Ser Cys Leu Ala Pro Ala Asp Thr Glu Gln Gln 230 1304 gat cac acg tct ccg aat gag aat gac cag gtc aca ccg caa cac cgg Asp His Thr Ser Pro Asn Glu Asn Asp Gln Val Thr Pro Gln His Arg gaa ccg gcc ggt ccc aac acc caa atc agg agt ggc tct gct cca cca 1352 Glu Pro Ala Gly Pro Asn Thr Gln Ile Arg Ser Gly Ser Ala Pro Pro 265 gca act cct gtg atg gtg cct gat tcc gcc gtg gcg agt gac aac agt 1400 Ala Thr Pro Val Met Val Pro Asp Ser Ala Val Ala Ser Asp Asn Ser 280 285 cca gtg acc cag ccg gcc ggc gag tgg tca gag ggc agc cag gct cac 1448 Pro Val Thr Gln Pro Ala Gly Glu Trp Ser Glu Gly Ser Gln Ala His 300 gte act ceg gtg gee get gte cet ggg cet gea geg etg eee tte etc 1496 Val Thr Pro Val Ala Ala Val Pro Gly Pro Ala Ala Leu Pro Phe Leu 310 tat gtc cct gga tct ccc act cag atg aat tct tac ggg cct gtg gtg 1544 Tyr Val Pro Gly Ser Pro Thr Gln Met Asn Ser Tyr Gly Pro Val Val 325 gcc ctt ccc aca gcg tcc cgt agt acc ctt gcc atg gac acc aca gga 1592 Ala Leu Pro Thr Ala Ser Arg Ser Thr Leu Ala Met Asp Thr Thr Gly 340 ctt cct gca cct ggc atg ctg ccc ttt tgc cat ctc tgg gta ccg gtg 1640 Leu Pro Ala Pro Gly Met Leu Pro Phe Cys His Leu Trp Val Pro Val 355 360

1688

ace cta gtg gct gct ggg gct gca cag cct gct gcc tcc atg gtc atg

Thr Leu Val Ala Ala Gly Ala Ala Gln Pro Ala Ala Ser Met Val Met

WO 01/55437 PCT/US01	/02623
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gac cca cag aat cta aca gat gtc tct ata ttc ctc ctc cta gaa gtc Asp Pro Gln Asn Leu Thr Asp Val Ser Ile Phe Leu Leu Leu Glu Val 25 30 35 40	269
tca ggg gat cca gaa ctg cag cca gtc ctt gct ggg ctg ttc ctg tcc Ser Gly Asp Pro Glu Leu Gln Pro Val Leu Ala Gly Leu Phe Leu Ser 45 50 55	317
atg tgc ctg gtc acg gtg ctg ggg aac ctg ctc atc atc ctg gcc atc Met Cys Leu Val Thr Val Leu Gly Asn Leu Leu Ile Ile Leu Ala Ile 60 65 70	365
age cet gae tee cae ete cae ace eee atg tae tte tte ete tee aac Ser Pro Asp Ser His Leu His Thr Pro Met Tyr Phe Phe Leu Ser Asn 75 80 85	413
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ctg act cag atg tct ctc ttt gcc att ttt gga ggc atg gaa gag aga Leu Thr Gln Met Ser Leu Phe Ala Ile Phe Gly Gly Met Glu Glu Arg 125 130 135	557
cat gct cct gag tgt gat ggc cta tga ctggt ttgtagccat ctgtcacccg His Ala Pro Glu Cys Asp Gly Leu * 140 145	609
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Ser Met Lys Trp Ser Tyr Lys Ser Gln Leu Asn Tyr Lys Thr Lys Gln
130 135 140 145

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150 155 160

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180 185 190

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			cac His 245											Gly		1844
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2510

2570 ′

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PCT/US01/02623 WO 01/55437

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cca aga gga ttc ctg agc tga ag tgcagatgac acattcaaag aagaactttc Pro Arg Gly Phe Leu Ser * 265	935
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85 90 95

			85					90					95			
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aat Asn	cag Gln 115	gtt Val	aac Asn	gag Glu	ctc Leu	atg Met 120	aat Asn	aga Arg	gtt Val	ctc Leu	ctt Leu 125	ttg Leu	act Thr	aca Thr	gaa Glu	440
gtt Val 130	ttt Phe	aga Arg	aaa Lys	cag Gln	ctg Leu 135	gat Asp	cct Pro	ttt Phe	cct Pro	cac His 140	aga Arg	cct Pro	gtt Val	cag Gln	tca Ser 145	488
cat His	ggt Gly	tta Leu	gat Asp	tgc Cys 150	act Thr	gat Asp	att Ile	aag Lys	gat Asp 155	acc Thr	att Ile	ggc	tct Ser	gtc Val 160	acc Thr	536
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	ttt Phe															632
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	gag Glu 275						Leu									920
	ttg Leu															968
	cct Pro															1016
	cca Pro			Lys	taa	tctc	att	taac	attg	ta a	tgca	agtt	c ta	caat	gata	1071
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546

606

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gggaaagett tgaagagaag gtgatgttea getatgtttg aagaatgggg agggeteate

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caatatgco	cc g											737
-210	)> 148											
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	L> CDS											
	2> (3).	. (1217)										
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ttt tgg (	ctc ttt	ctc ctg	ctg ctg	ctc	ccg	ggc	gcg	CCC	gac	cca	cgc	95
Phe Trp 1	Leu Pne	20	Leu Leu	Leu	25	GIY	AIA	PIO	Asp	30	Arg	
gtc cgc (	tcc agg	ccg tgg	gag gga	acc	gac	gag	ccg	ggc	tcg	gcc	tgg Trp	143
var Arg	35	PIO IIP	GIU GI	40	пор	O.Lu	110	017	45			
gcc tgg (	ccg ggc	ttc cag	cgc ctg	cag	gag	cag Gln	ctc	agg Arg	gcg Ala	gcg Ala	ggt Glv	191
Ala IIP	50	rne orn	55					60			<b>-</b>	
gcc ctc Ala Leu	tcc aag Ser Lys	cgg tac	tgg acg	ctc Leu	ttc Phe	agc Ser	tgc Cys	cag Gln	gtg Val	tgg Trp	ccc Pro	239
65	•	<b>J</b> -	70				75					
gac gac Asp Asp	tgt gac Cys Asp	gag gac Glu Asp	gag gag Glu Glu	gca Ala	gcc Ala	acg Thr	ggg ggg	ccc Pro	ctg Leu	ggc Gly	tgg Trp	287
80		85				90					95	
cgc ctt Arg Leu	cct ctg Pro Leu	ttg ggc Leu Gly	cag cgg	tac Tyr	ctg Leu	gac Asp	ctc Leu	ctg Leu	acc Thr	acg Thr	tgg Trp	335
		100			105					110		
tac tgc Tyr Cys	agc ttc Ser Phe	aaa gac Lys Asp	Cys Cys	Pro	aga Arg	gjy ggg	gat Asp	tgc Cys	Arg	atc Ile	tcc Ser	383
	115			120					125			
aac aac Asn Asn	Phe Thr	ggc tta Gly Leu	Glu Tr	Asp	ctg Leu	aat Asn	gtg Val	Arg	Leu	His	ggc Gly	431
	130		139					140			<b></b>	470
cag cat Gln His			Leu Val				Val					479
145			150				155	• • •			<b>.</b>	527
gag acg		Pro Glu				Leu						527
160	.a. ~~-	165	***		a~~	170	at ~	ata	asa	220		575
tct ggc Ser Gly												373

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atc ttc gat gas Ile Phe Asp Glu 240	a gcg gag aag 1 Ala Glu Lys 245	ctg cac cca Leu His Pro	ggg ctg ctg gag Gly Leu Leu Glu 250	gtc ctt 767 Val Leu 255
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cca tgg act atc Pro Trp Thr Ilc 27	e Phe Leu Phe	ctc agt aat Leu Ser Asn 280	ctc agg ggc gat Leu Arg Gly Asp 285	ata atc 863 Ile Ile
aat gag gtg gt Asn Glu Val Va 290	c cta aag ttg l Leu Lys Leu	ctc aag gct Leu Lys Ala 295	gga tgg tcc cgg Gly Trp Ser Arg 300	gaa gaa 911 Glu Glu
att acg atg ga Ile Thr Met Gl 305	a cac ctg gag u His Leu Glu 310	ccc cac ctc Pro His Leu	cag gcg gag att Gln Ala Glu Ile 315	gtg gag 959 Val Glu
acc ata gac aa Thr Ile Asp As 320	t ggc ttt ggc n Gly Phe Gly 325	cac agc cgt His Ser Arg	ctt gtg aag gaa Leu Val Lys Glu 330	aac ctg 1007 Asn Leu 335
att gac tac tt Ile Asp Tyr Ph	c atc ccc ttc e Ile Pro Phe 340	ctg cct ttg Leu Pro Leu 345	gag tac cgt cac Glu Tyr Arg His	gtg agg 1055 Val Arg 350
ctg tgt gca cg Leu Cys Ala Ar 35	g Asp Ala Phe	ctg agc cag Leu Ser Glr 360	ggag ctc ctg tat Glu Leu Leu Tyn 369	Lys Glu
gag aca ctg ga Glu Thr Leu As 370	it gaa ata gcc sp Glu Ile Ala	cag atg atg Gln Met Met 375	g gtg tat gtc ccc : Val Tyr Val Pro 380	e aag gag 1151 o Lys Glu
gaa caa ctc tt Glu Gln Leu Ph 385	t tot too cag ne Ser Ser Glr 390	Gly Cys Lys	g tot att too cag s Ser Ile Ser Gli 395	g agg att 1199 n Arg Ile
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10 15 20

53

ata tgt att gcg aat agt gag att tat tac aca gtc cta aca ttg atg

Ile Cys Ile Ala Asn Ser Glu Ile Tyr Tyr Thr Val Leu Thr Leu Met

25 30 35

cag ttt agt tgc ttg tgg atg gtg ttg tca gga aaa aag gta ata ttt

Gln Phe Ser Cys Leu Trp Met Val Leu Ser Gly Lys Lys Val Ile Phe

45 50 55

tct tct gaa ctc atg gtt aga aag ggc agg aga agc tgg aag taa gat 245 Ser Ser Glu Leu Met Val Arg Lys Gly Arg Arg Ser Trp Lys \*

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Glu Phe Leu Ser Leu Leu Cys Leu Gly Leu Cys Leu Gly Tyr Glu Asp
5 10 15

gag aaa aag aat gag aaa ccg ccc aag ccc tcc ctc cac gcc tgg ccc
Glu Lys Lys Asn Glu Lys Pro Pro Lys Pro Ser Leu His Ala Trp Pro
20 25 30 35

age teg gtg gtt gaa get gag age aat gtg ace etg aag tgt eag get

Ser Ser Val Val Glu Ala Glu Ser Asn Val Thr Leu Lys Cys Gln Ala

40

45

50

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					aca Thr											369
tac Tyr	aag Lys	cag Gln 70	gaa Glu	cag Gln	agc Ser	tcg Ser	gca Ala 75	gaa Glu	aac Asn	gaa Glu	gct Ala	gaa Glu 80	ttc Phe	ccc Pro	ttc Phe	417
acg Thr	gac Asp 85	ctg Leu	aag Lys	cct Pro	aag Lys	gat Asp 90	gct Ala	gly aaa	agg Arg	tac Tyr	ttt Phe 95	tgt Cys	gcc Ala	tac Tyr	aag Lys	465
					gag Glu 105											513
gtg Val	gtc Val	aca Thr	gat Asp	aaa Lys 120	cac His	gat Asp	gaa Glu	ctt Leu	gaa Glu 125	gct Ala	ccc Pro	tca Ser	atg Met	aaa Lys 130	aca Thr	561
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					gtc Val											657
					tcc Ser											705
					gag Glu 185											753
					ccc Pro											801
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		-			gca	-			tag *	c a	aaaa	gaca	g cc	ctgg	ccac	900
taa	agga	ggg s	ggga	tegt	gc t	ggcc	aagg	t ta	tegga	aaat	ctg	gaga	tgc :	agat	actgtg	960
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ccc ctg ctg aca ctc tac ctg ctc ctc ttc tgg ctc tca ggc tac tcc Pro Leu Leu Thr Leu Tyr Leu Leu Leu Phe Trp Leu Ser Gly Tyr Ser 5 10 15	164
att gtc act caa atc acc ggt cca aca aca gtg aat ggc ttg gag cgg Ile Val Thr Gln Ile Thr Gly Pro Thr Thr Val Asn Gly Leu Glu Arg 20 25 30	212
ggc tcc ttg acc gtg cag tgt gtt tac aga tca ggc tgg gag acc tac Gly Ser Leu Thr Val Gln Cys Val Tyr Arg Ser Gly Trp Glu Thr Tyr 35 40 45	260
ttg aag tgg tgg tgt cga gga gct att tgg cgt gac tgc aag atc ctt Leu Lys Trp Trp Cys Arg Gly Ala Ile Trp Arg Asp Cys Lys Ile Leu 50 65	308
gtt aaa acc agt ggg tca gag cag gag gtg aag agg gac cgg gtg tcc Val Lys Thr Ser Gly Ser Glu Gln Glu Val Lys Arg Asp Arg Val Ser 70 75 80	356
atc aag gac aat cag aaa aac cgc acg ttc act gtg acc atg gag gat Ile Lys Asp Asn Gln Lys Asn Arg Thr Phe Thr Val Thr Met Glu Asp 85 90	404
ctc atg aaa act gat gct gac act tac tgg tgt gga att gag aaa act Leu Met Lys Thr Asp Ala Asp Thr Tyr Trp Cys Gly Ile Glu Lys Thr 100 105 110	452
gga aat gac ctt ggg gtc aca gtt caa gtg acc att gac cca gcg tcg Gly Asn Asp Leu Gly Val Thr Val Gln Val Thr Ile Asp Pro Ala Ser 115 120 . 125	500
act cct gcc ccc acc acg cct acc tcc act acg ttt aca gca cca gtc Thr Pro Ala Pro Thr Thr Pro Thr Ser Thr Thr Phe Thr Ala Pro Val 130 145	548
acc caa gaa gaa act agc agc tcc cca act ctg acc ggc cac cac ttg Thr Gln Glu Glu Thr Ser Ser Pro Thr Leu Thr Gly His His Leu 150 155 160	596
gac aac agg cac aag ctc ctg aag ctc agt gtc ctc ctg ccc ctc atc Asp Asn Arg His Lys Leu Leu Lys Leu Ser Val Leu Leu Pro Leu Ile 165 170 175	644
ttc acc ata ttg ctg ctg ctt ttg gtg gcc gcc tca ctc ttg gct tgg Phe Thr Ile Leu Leu Leu Leu Val Ala Ala Ser Leu Leu Ala Trp 180 185 190	692
agg atg atg aag tac cag cag aaa gca gcc ggg atg tcc cca gag cag Arg Met Met Lys Tyr Gln Gln Lys Ala Ala Gly Met Ser Pro Glu Gln 195 200 205	740
gta ctg cag ccc ctg gag ggc gac ctc tgc tat gca gac ctg acc ctg Val Leu Gln Pro Leu Glu Gly Asp Leu Cys Tyr Ala Asp Leu Thr Leu 210 215 220 225	788

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			at gtc acc atg Yr Val Thr Met	
			tg acc ttg ggt eu Thr Leu Gly 270	
			ac ctc agt agc is Leu Ser Ser 285	
			ac agc acc atc Tyr Ser Thr Ile 300	
tagcctgcac	tecaggetee tt	cttggacc ccag	gctgtg agcacact	cc tgcctcatcg 1088
accgtctgcc	ccctgctccc ct	catçagga ccaa	cccggg gactggtg	cc tctgcctgat 1148
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atgctctggg	gctttcatgg ga	atgatgaa gatg	ataatg agaaaaat	gt tatcattatt 1328
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gaa gco Glu Ala 75	Ser	tgg Trp	gly aaa	agg Arg	gcc Ala 80	agc Ser	agc Ser	cgg Arg	cca Pro	gca Ala 85	gcc Ala	ccc Pro	act Thr	cct Pro	351
ccc ato Pro Met 90	cca Pro	gcc Ala	aac Asn	gta Val 95	cag Gln	gcc Ala	gga Gly	tgg Trp	gaa Glu 100	cag Gln	tct Ser	gtg Val	agg Arg	ctt Leu 105	399
ttg tgo Leu Cys	cac His	tcc Ser	tgg Trp 110	ctg Leu	cgc Arg	ttg Leu	gca Ala	gct Ala 115	ctg Leu	cat His	gtc Val	aca Thr	cat His 120	gag Glu	447
gaa too Glu Se:	-	gtc	tcaa	aat	ggcc	cag (	gaat	ccag	ca t	gagc	tgtg	c ta	ggag	tcaa	503
gaggtt	gcc	acga	ctgg	gc t	tggt	tcct	t gt	tcat	gagc	gag	cacg	tcc	ctca	gtctat	563
ccatct	agct	ggtg	acgt	tt c	ctga	acac	c ag	ggga	gacc	agg	ctct	gtt	ctag	gcacgg	623
gcagca	gtga	ggaa	gact	gc a	cggc	ccct	g aa	gcta	gtgc	tgg	ggga	cag	ggtt	ggggtg	683
gcatgg	ccct	cato	acca	gc c	gcct	gcga	g tc	tgtg	ccag	agc	agat	tgg	ggtg	acaaca	743
gactgc	actg	tgtg	gggt	ga g	gggc	agca	t gt	ggct	ggcc	ccc	aaat	gag	ggga	gatatg	803
gttagg	gagg	cacc	ttgg	ec t	gttg	gcaa	t gg	gtgg	gaa						842
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act gta tat ctt ttc tat ctt ctt aga agt aat ata tgg ctg gaa atg

Thr Val Tyr Leu Phe Tyr Leu Leu Arg Ser Asn Ile Trp Leu Glu Met

Met Ser Gln Gln Ser Trp Phe

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WO 01/55437 PC1/US01.	702023
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acc agt aat tat ttt agt tag ct teacagatet etetteettg ettgttettg Thr Ser Asn Tyr Phe Ser $*$ 40	560
agagegagge tttttagtag gaagagaaat tgtetaaaae gattaataae cacaaattea	620
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gag gtg cag ctg gtg gag tct ggc gga ggc ttg gta aag ccg ggg ggg Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly 20 25 30 35	153
tot ott agg otc toc tgt goa goo tot gga tto agt tto agt aaa goo Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Lys Ala 40 45 50	201
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ggc cgc att aaa act aag aaa gat gct ggg aca aca gac tac gct gca Gly Arg Ile Lys Thr Lys Lys Asp Ala Gly Thr Thr Asp Tyr Ala Ala 70 75 80	297
ccc gtg aaa ggc aga ttc acc atc tca aga gat gat tca gaa aat acg	345

393

ccc gtg aaa ggc aga ttc acc atc tca aga gat gat tca gaa aat acg Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Glu Asn Thr

tta cat ctg caa ctg aac agc ctg aaa acc gaa gac aca ggc ata tat

PCT/US01/02623 WO 01/55437 Leu His Leu Gln Leu Asn Ser Leu Lys Thr Glu Asp Thr Gly Ile Tyr 110 105 tat tgt tgt aca gac ccc acc tgg tac gcg gct gtg ggt ggc tcc tac 441 Tyr Cys Cys Thr Asp Pro Thr Trp Tyr Ala Ala Val Gly Gly Ser Tyr 125 120 tgg ggc cag gga acc ctg gtc acc gtc tcc tca gcc tcc acc aag ggc 489 Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly 140 cca tcg gtc ttc ccc ctg gca ccc tcc tcc aag agc acc tct ggg ggc 537 Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly aca geg gee etg gge tge etg gte aag gae tae tte eee gaa eeg gtg 585 Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val acg gtg tcg tgg aac tca ggc gcc ctg acc agc ggc gtg cac acc ttc 633 Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe 190 185 ceg get gte eta cag tee tea gga ete tae tee ete age age gtg gtg 681 Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val 200 205 acc gtg ccc tcc agc agc ttg ggc acc cag acc tac atc tgc aac gtg 729 Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val 220 215 780 aat cac aag cct gta ttg cgg gcg ctc tag a ggatcaagct tacgtacgcg Asn His Lys Pro Val Leu Arg Ala Leu \* 230 793 tgataggcct atc <210> 159 <211> 1644 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (66)..(1499) <400> 159 agcccagcac tagaagtcgg cggtgtttcc attcggtgat cagcactgaa cacagaggac 60 atg gag ttt ggg ctg agc tgg gtt ttc ctc gtt gct ctt tta 107 tcacc Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Leu Leu aga ggt gtc cag tgt cag gtg cag ctg gtg gag tct ggg gga ggc gtg 155 Arg Gly Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Val 203 gte cag cet ggg agg tee etg aga ete tee tgt gea geg tet gga tte Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe

					ggc Gly												251
GJA GGA	ctg Leu	gag Glu 65	tgg Trp	gtg Val	gca Ala	gct Ala	ata Ile 70	tgg Trp	tat Tyr	gat Asp	gga Gly	agt Ser 75	aat Asn	aaa Lys	tac Tyr		299
tat Tyr	gca Ala 80	gac Asp	tcc Ser	gtg Val	aag Lys	ggc Gly 85	cga Arg	ttc Phe	acc Thr	atc Ile	tcc Ser 90	aga Arg	gac Asp	aat Asn	tcc Ser		347
aag Lys 95	aac Asn	acg Thr	ttg Leu	tat Tyr	atg Met 100	caa Gln	atg Met	aac Asn	agc Ser	ctg Leu 105	aga Arg	gcc Ala	gag Glu	gac Asp	acg Thr 110		395
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					tac Tyr												491
					gcc Ala												539
_				_	agc Ser											•	587
					ttc Phe 180												635
					ggc												683
					ctc Leu	_	_							-			731
					tac Tyr												779
					aga Arg												827
	_		_	_	cca Pro 260	_		_		-			-		_		875
					aaa Lys		_	_			_						923
		-		_	gtg Val			_		_		_	-				971

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tcc Ser	aaa Lys	gcc Ala	aaa Lys 370	Gly	cag Gln	ccc Pro	cga Arg	gaa Glu 375	cca Pro	cag Gln	gtg Val	tac Tyr	acc Thr 380	ctg Leu	ccc Pro	1211
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gac Asp	ggc	tcc Ser	ttc Phe	ttc Phe	Lev	tat Tyr	ago Ser	aag Lys	ctc Leu 440	Thr	gtg Val	gac	aag Lys	agc Ser 445	Arg	1403
tgg Trp	cag Gln	cag Glr	999 Gly 450	Asn	gto Val	tto Phe	tca Ser	tgc Cys 455	Ser	gtg Val	atg Met	cat His	gag Glu 460	Ala	ctg Leu	1451
			Tyr					Leu					Gly		tga *	1499
gto	gcgac	ggc	cggc	caago	ccc c	eget	cccc	g gg	rctct	cgcg	gto	gcac	gag	gatg	cttggc	1559
acg	jtaco	ccg	tcta	acata	act t	ccca	aggca	ac co	agca	tgga	aat	aaag	ıcac	ccac	cactgc	1619
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		_														
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caa Gln	aac Asn	ctg Leu	tca Ser 260	gtg Val	att Ile	Gly ggg	ttc Phe	cga Arg 265	atc Ile	ctc Leu	ctc Leu	ctg Leu	aaa Lys 270	gtg Val	gcc Ala	816
Gl y GG 9	ttt Phe	aat Asn 275	Leu	ctc Leu	atg Met	acg Thr	ctg Leu 280	cgg Arg	ctg Leu	tgg Trp	gtc Val	cag Gln 285	ctg Leu	aga Arg	tct Ser	864
	aga Arg 290	Leu		gga	cag	cctg	tgc	tccc	tege	tc c	ttcc	tctg	g ca	ttgc	ccct	919
ctt	ctcc	ctc	tcca	aaca	ga g	<b>9</b> 999	aact	t ct	tcct	tacc	ccc	aagg	gag	ggtg.	aaagct	979
ggo	ettac	сса	cttt	tgtg	gc c	cccc	ccgg	g ca	attg	ccac	cca	attg	ggt	tcct	tacccc	1039
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<212> DNA

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (179)..(322)

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60

682

ctttcatttt ctttactttg tttttttag aagaggtgcg aggtcctggg ccccagaggt

a 683

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W O 01/33	9431												•	CITOS	01/02025
Leu-Glu 2	Ala .	Asn	Gly 175	Arg	Lys	Val	Arg	Gly 180	Gly	Leu	Pro	Leu	Val 185	Thr	
tgt gcc Cys Ala	Leu .	_			-				-	-		_			748
agg gac Arg Asp															796
gcc atc Ala Ile 220															844
gcc tgg Ala Trp 235															892
ctg atg Leu Met															940
agc tac Ser Tyr															988
ctg gtg Leu Val															1036
gct gcc Ala Ala 300			_	_	_	_		_	_			_			1084
tac gca Tyr Ala 315															1132
ttc acc Phe Thr															1180
ctg ttc Leu Phe															1228
gcc gct Ala Ala							cgg	tggg	gct	9999	cctg	ga g	gccc	agata	1282
cagcacat	cc a	CCC	aggt	cc c	gage	cctc	a ca	ccct	ggac	aaa	aagg	gac	aget	gcatt	c 1342
cagagcag	gga g	gca	gggc	tc t	3 <b>3</b> 33	ccag	a at	ggct	gtcc	ttg	tcgt	aga	gccc	tccac	a 1402
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gtgatcat	ag c	ctca	ctgc	ac c	ctca	acct	c ct	gggt	tcaa	gca	atcc	tcc	tgcc	tcagc	c 1522
tcctgaac															
agagacag								•							
tcccacgt	gg g	cct	ccca	aa a	cgct	ggaa	c ta	caag	tgtg	agc	cacc	gcg	ccct	ggccc	a 1702

agccctccac attttcaatc caggaagcct tgagtctgtg ttgtgtcctg acacctccaa 1762
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WO 0	1/554	137												F	CT/US01/0	2623
	1	15					120					125				
tgc ca Cys Gl	ag c ln L 30	tg eu	cta Leu	aag Lys	atc Ile	atc Ile 135	gat Asp	tta Leu	ggt Gly	ggc Gly	tgc Cys 140	tta Leu	agt Ser	att Ile	act Thr	730
gat gt Asp Va 145	tg t al S	cc er	tta Leu	cat His	gca Ala 150	tta Leu	gga Gly	aaa Lys	aac Asn	tgc Cys 155	cca Pro	ttt Phe	ttg Leu	cag Gln	tgt Cys 160	778
gtc ga Val A	ac t .sp I	tt Phe	tca Ser	gct Ala 165	act Thr	cag Gln	gta Val	tct Ser	gac Asp 170	agt Ser	ggt Gly	gtg Val	att Ile	gca Ala 175	ctt Leu	826
gtt ag Val S	gt g er (	gga Gly	cct Pro 180	tgt Cys	gcg Ala	aag Lys	aaa Lys	tta Leu 185	gag Glu	gag Glu	att Ile	cat His	atg Met 190	gga Gly	cat His	874
tgt g Cys V	al i	aat Asn 195	ctg Leu	act Thr	gat Asp	Gly ggg	gct Ala 200	gtc Val	gaa Glu	gct Ala	gtc Val	ctt Leu 205	act Thr	tac Tyr	tgt Cys	922
cct c Pro G	aa Sln 210	ata Ile	cgt Arg	ata Ile	tta Leu	ctc Leu 215	ttc Phe	cat His	gga Gly	tgc Cys	ccc Pro 220	ttg Leu	ata Ile	aca Thr	gat Asp	970
cat t His S 225	ser .	cga Arg	gaa Glu	gtg Val	ttg Leu 230	gag Glu	caa Gln	tta Leu	gta Val	ggc Gly 235	Pro	aac Asn	aaa Lys	cta Leu	aag Lys 240	1018
caa g Gln V	gtg Val	aca Thr	tgg Trp	act Thr 245	Val	tat Tyr	tga *	tgc	tttt	ttg	aaga	tgat	ca a	tgct	aggaa	1072
agctt	tatc	aa	aact	actt	tc c	cagg	aaac	c at	ctat	agag	att	tgca	ttc	tact	taatgt	1132
taaca	acta	tt	ttta	atta.	tt t	tatt	gtct	t aa	ıgtta	taac	tct	caga	gaa	ttag	ctaagt	1192
cttgg	gtat	at	acat	ggtt	tg t	gctt	tact	c tt	aaac	atct	. tta	aagt	gct	atta	ttctat	1252
atct	gttg	ıga	tgag	tcat	ta t	ttt	gaaa	at ga	taat	ccta	gca	tgaa	ctc	tgat	ctatgg	1312
tgtt	ggat	tc	tgtt	tett	aa a	taad	ettta	aa aa	ttaa	ctgt	tt:	ccct	tga	gatt	tccttc	1372
teeta	atgt	ag	gtat	ttga	igc t	att	gttct	ta aç	gttta	cctg	g taa	igtat	aaa	cctt	gggaga	1432
atct	aagt	aa	acat	attt	ct a	aaag	gcata	ag ti	cacct	tcct	att	ttct	ggc	tctt	accttc	1492
ttgg	agta	att	taaa	tgc	ca t	ttg	ccaaa	aa go	cagao	ctga	a aca	atcaa	gcc	tggt	taattc	1552
ntca	aaga	aat	ttag	9999	att ç	gtti	ccc	cg ga	aaatq	ggagt	ga g	ettat	tag	ccat	tcagcg	1612
gtat	tagg	gaa	taca	agagg	gct (	ettg	cca	ge e	acato	ccant	c cc	attgi	ittt	taa	ggggact	1672
cctc	ccag	ggt	acat	ttta	aag g	gcac	ggt	ag c	nttc	cctc	c cta	aggca	aaat	tgc	atccnaa	1732
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235 ·

agc atc aga gat gcc aga aga agt gat gcg ggg aga tac ttc ttt cgt Ser Ile Arg Asp Ala Arg Arg Ser Asp Ala Gly Arg Tyr Phe Phe Arg

atg gag aaa gga agt ata aaa tgg aat tat aaa cat cac cgg ctc tct

210

672

***	UI, U															
Met 225	Glu	Lys	Gly	Ser	11e 230	Lys	Trp	Asn	Tyr	Lys 235	His	His	Arg	Leu	Ser 240	
					ttg Leu											768
acc Thr	ctg Leu	gag Glu	tcc Ser 260	ggc Gly	tgc Cys	ccc Pro	cag Gln	aat Asn 265	ctg Leu	acc Thr	tgc Cys	tct Ser	gtg Val 270	ccc Pro	tgg Trp	816
gcc Ala	tgt Cys	gag Glu 275	cag Gln	gly ggg	aca Thr	ccc Pro	cct Pro 280	atg Met	atc Ile	tcc Ser	tgg Trp	ata Ile 285	GJA aaa	acc Thr	tcc Ser	864
gtg Val	tcc Ser 290	ccc Pro	ctg Leu	gac Asp	ccc Pro	tcc Ser 295	acc Thr	acc Thr	cgc Arg	tcc Ser	tcg Ser 300	gtg Val	ctc Leu	acc Thr	ctc Leu	912
atc Ile 305	cca Pro	cag Gln	ccc Pro	cag Gln	gac Asp 310	cat His	ggc Gly	acc Thr	agc Ser	ctc Leu 315	acc Thr	tgt Cys	cag Gln	gtg Val	acc Thr 320	960
ttc Phe	cct Pro	gly ggg	gcc Ala	agc Ser 325	gtg Val	acc Thr	acg Thr	aac Asn	aag Lys 330	acc Thr	gtc Val	cat His	ctc Leu	aac Asn 335	gtg Val	1008
tcc Ser	tac Tyr	ccg Pro	cct Pro 340	cag Gln	aac Asn	ttg Leu	acc Thr	atg Met 345	act Thr	gtc Val	ttc Phe	caa Gln	gga Gly 350	gac Asp	ggc	1056
aca Thr	gta Val	tcc Ser 355	Thr	gtc Val	ttg Leu	gga Gly	aat Asn 360	Gly	tca Ser	tct Ser	ctg Leu	tca Ser 365	ctc Leu	cca Pro	gag Glu	1104
		Ser			ctg Leu		Cys									1152
ccc Pro 385	Pro	gcc Ala	agg Arg	ctg Leu	agc Ser 390	Leu	agc Ser	tgg Trp	aga Arg	ggc Gly 395	Leu	acc	ctg Leu	tgc Cys	ccc Pro 400	1200
			Ser	Asn	ccg Pro	Gly	Val		Glu	Leu	Pro	Trp	Val		Leu	1248
agg Arg	gat	gaa Glu	gct Ala 420	Glu	ttc Phe	acc Thr	tgc Cys	aga Arg 425	Ala	cag Gln	aac Asn	cct Pro	ctc Leu 430	Gly	tct Ser	1296
			Tyr		aac Asn			Leu					Thr		gga Gly	1344
		Glr			gtc Val		Gly					Ala			ttc Phe	1392
_	Ser		_	_		Phe	_	-			Ser	_	-		aaa Lys 480	1440
tcg	gca	agg	r cca	gca	gcg	ggc	gtg	gga	gat	acg	ggo	ata	gag	gat	gca	1488

Ser	Ala	Arg	Pro	Ala 485	Ala	Gly	Val	Gly	Asp 490	Thr	Gly	Ile	Glu	Asp 495	Ala	
														cct Pro		1536
														cgc Arg		1584
														cag Gln	atg Met	1632
														gag Glu		1680
-			_	atc Ile 565		_	_	gaa	actg	cag a	agacı	tcac	cc t	gatto	gaggg	1734
atc	acag	ccc (	ctcc	aggc	aa g	ggag	aagt	c aga	agge	tgat	tct	tgta	gaa	ttaa	cagccc	1794
tca	acgt	gat o	gagc	tatg	at a	acac	tatg	a at	tatg	tgca	gagi	tgaa	aag	caca	caggct	1854
tta	gagt	caa a	agta	tctc	aa a	cctg	aatc	c ac	actg	tgcc	ctc	cctt	tta	tttt	tttaac	1914
taa	aaga	cag a	acaa	attc	ct a	cctc										1939

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Phe Gly Leu Ala Leu Gln Leu Ile Leu Asp Leu Lys Leu Thr Thr Val  5 10 15	643
aac cag cga gaa agt gat gtg gca aga gtt gcc acg gct gaa gaa tat Asn Gln Arg Glu Ser Asp Val Ala Arg Val Ala Thr Ala Glu Glu Tyr 20 25 30	691
tca aag aaa ggt ctg ctt gga cag gaa aca ctt cat gct gga tca cag Ser Lys Lys Gly Leu Leu Gly Gln Glu Thr Leu His Ala Gly Ser Gln 35 40 45 50	739
aca aga atg cag att ctt atc tcc tga gaccc cttgaattcc accgcaagtg Thr Arg Met Gln Ile Leu Ile Ser * 55	791
g	792
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attatcagta ataatcataa ttgtt atg tta aaa tta ttg tgt gcc gca gag Met Leu Lys Leu Cys Ala Ala Glu 1 5	232
gta aca aat gtc ctt ttc aac tgt gtt ttt gac tat ggc tgt cct aaa Val Thr Asn Val Leu Phe Asn Cys Val Phe Asp Tyr Gly Cys Pro Lys 10 20 25	280
act ttt tgt cat cca tgg aca att ttt gtc ttg ttt tgg tcc tct tta Thr Phe Cys His Pro Trp Thr Ile Phe Val Leu Phe Trp Ser Ser Leu	328
30 35 40	
	376
gaa ggt ggc ttt ata atc agc tac aaa act cta aca ggt gct ctt gaa Glu Gly Gly Phe Ile Ile Ser Tyr Lys Thr Leu Thr Gly Ala Leu Glu	376 425
gaa ggt ggc ttt ata atc agc tac aaa act cta aca ggt gct ctt gaa Glu Gly Gly Phe Ile Ile Ser Tyr Lys Thr Leu Thr Gly Ala Leu Glu 45 50 55  tgc agg ttt ctg ata act ttg gag att gtg aca tca gaa tag aggaaaa Cys Arg Phe Leu Ile Thr Leu Glu Ile Val Thr Ser Glu *	
gaa ggt ggc ttt ata atc agc tac aaa act cta aca ggt gct ctt gaa Glu Gly Gly Phe Ile Ile Ser Tyr Lys Thr Leu Thr Gly Ala Leu Glu 45 50 55  tgc agg ttt ctg ata act ttg gag att gtg aca tca gaa tag aggaaaa Cys Arg Phe Leu Ile Thr Leu Glu Ile Val Thr Ser Glu *	425

atacttccat aaacaaaget, tgcagcctat ttgttgctct ttaactgact tctgccgaat 665
tcgcacacta ttcgctcgca ctccctactc atcggccctc cggcaatacc ccacccggcc 725
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Leu Leu Ile Ser Ser Gly Cys Ala Leu Tyr Pro Leu Gly Trp Asn Ser

130 135 140 ccg gag ata atg caa aca tgt ggg aat gtc tcc aat caa ttt cag tta 720 Pro Glu Ile Met Gln Thr Cys Gly Asn Val Ser Asn Gln Phe Gln Leu 150 768 ggt acc tgt cgg ctt ggc tgg gcc tat tac tgt gct gga ggt gga aca Gly Thr Cys Arg Leu Gly Trp Ala Tyr Tyr Cys Ala Gly Gly Gly Thr 165 cct gca gcc atg ttg atc tgc ccc tgg ctc tct tgc ttt gct gga aga 816 Pro Ala Ala Met Leu Ile Cys Pro Trp Leu Ser Cys Phe Ala Gly Arg 185 aac ccc cag cct gtc ata ttg ggg ggg aag cac cat gag.gaa aac cac 864 Asn Pro Gln Pro Val Ile Leu Gly Gly Lys His His Glu Glu Asn His 200 195 ttc tta tgc tat gga gct tgg cca ttg ccc tca acc ctt gag ctt cga 912 Phe Leu Cys Tyr Gly Ala Trp Pro Leu Pro Ser Thr Leu Glu Leu Arg aaa gaa gac cgg ggg ggg cgg gca aca ggg aag caa gtg acc ccc caa 960 Lys Glu Asp Arg Gly Gly Arg Ala Thr Gly Lys Gln Val Thr Pro Gln 230 cca ctt aga ttc cat gtc tct act tgg atg tct agt aga ctt gac aga 1008 Pro Leu Arg Phe His Val Ser Thr Trp Met Ser Ser Arg Leu Asp Arg gtg tac ata tcc ata acc aag atc caa atc ttc caa tcc taa acccat 1056 Val Tyr Ile Ser Ile Thr Lys Ile Gln Ile Phe Gln Ser \*

265

260

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Met Lys Ser Ser Leu Thr Val Val Gly Thr Leu Trp

1 5 10

gcc ttc ctg tcc ctt gtt act gct gtg acc agt tct acc agt tac ttc

Ala Phe Leu Ser Leu Val Thr Ala Val Thr Ser Ser Thr Ser Tyr Phe

15 20 25

cta cct tac tgg ctc ttt gga tcc cag atg ggg aag cca gtg tca ttc

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ctg Leu	atc Ile	atg Met	gtg Val	gaa Glu 65	gaa Glu	tgt Cys	GJA aaa	cgc Arg	tat Tyr 70	gcc Ala	agc Ser	ttc Phe	aat Asn	gcc Ala 75	atc Ile		300
cca Pro	agc Ser	ctg Leu	gcc Ala 80	tgg Trp	cag Gln	atg Met	tgc Cys	aca Thr 85	gtg Val	gtg Val	aca Thr	ggt Gly	gcc Ala 90	ggc Gly	tgt Cys		348
gct Ala	ctg Leu	ctg Leu 95	ctc Leu	ctg Leu	gag Glu	tca Ser	cta Leu 100	gct Ala	gct Ala	gtc Val	ctg Leu	ggt Gly 105	tgc Cys	tgc Cys	atg Met		396
gag Glu	gag Glu 110	ctc Leu	atc Ile	tcc Ser	aga Arg	atg Met 115	atg Met	gga Gly	cgt Arg	tgc Cys	atg Met 120	gga Gly	gca Ala	gcg Ala	cag Gln		444
ttt Phe 125	gtt Val	gga Gly	ggt Gly	cca Pro	atg Met 130	cag Gln	ccc Pro	ttc Phe	tgt Cys	gaa Glu 135	gcc Ala	ttc Phe	cct Pro	gat Asp	cta Leu 140		492
ctt Leu	ttg Leu	aca Thr	tct Ser	tta Leu 145	gca Ala	gat Asp	atg Met	aac Asn	gat Asp 150	cct Pro	gta Val	act Thr	cca Pro	aga Arg 155	gga Gly		540
ata Ile	tgg Trp	ggt Gly	aga Arg 160	atg Met	aat Asn	ggc Gly	GJ A BBB	ggc Gly 165	tgg Trp	Gly 999	ggt Gly	ggg Gly	ctg Leu 170	ctg Leu	ata Ile		588
	tca Ser																636
atg Met	caa Gln 190	aca Thr	tgt Cys	GJ À aaa	aat Asn	gtc Val 195	tcc Ser	aat Asn	caa Gln	ttt Phe	cag Gln 200	tta Leu	ggt Gly	acc Thr	tgt Cys		684
	ctt Leu																732
	ttg Leu																780
	gtc Val								Arg					Tyr			828
-	gag Glu		_		_				_	gc	tttg	aaag	a ag	attg	gaga		879
999	ttgg	gaa	nggg	gaag	ga g	ggag	ccct	g aa	aaag	aagg	tac	ntag	ggt	ttaa	ggcca	t	939
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W	0 01/5	5437												,	PC17U	S01/02623
180					185					190					195	
			aag Lys													740
-	_		gag Glu 215			-		_			-	-		_		788
			agc Ser													836
	-		atc Ile	_			_	_					-	_		· 884
			cag Gln													932
	_		cac His		_	_	_	_			_			-	-	980
_			gag Glu 295		-	_					-			-	_	1028
			gac Asp			-		_		_	_				_	1076
			agc Ser						_	_						1124
	_		gag Glu					_					_		-	1172
			ctc Leu		-						-					1220
			cgc Arg 375													1268
_			gag Glu		_		_	_	_	_	_	_			_	1316
acc . Thr			gtg Val													1364
			tgc Cys													1412
			ggc Gly													1460

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440 445 450	
aac cca act gtg tgg ccg gat cct gag gtc tac gac ccc ttc cgc ttt Asn Pro Thr Val Trp Pro Asp Pro Glu Val Tyr Asp Pro Phe Arg Phe 455 460 465	1508
gac cca gag aac agc aag ggg agg tca cct ctg gct ttt att cct ttc Asp Pro Glu Asn Ser Lys Gly Arg Ser Pro Leu Ala Phe Ile Pro Phe 470 475 480	1556
tcc gca ggg ccc agg aac tgc atc ggg cag gcg ttc gcc atg gcg gag Ser Ala Gly Pro Arg Asn Cys Ile Gly Gln Ala Phe Ala Met Ala Glu 485 490 495	1604
atg aaa gtg gtc ctg gcg ttg atg ctg ctg cac ttc cgg ttc ctg cca Met Lys Val Val Leu Ala Leu Met Leu His Phe Arg Phe Leu Pro 500 505 510 515	1652
gac cac act gag ccc cgc agg aag ctg gaa ttg atc atg cgc gcc gag Asp His Thr Glu Pro Arg Arg Lys Leu Glu Leu Ile Met Arg Ala Glu 520 525 530	1700
ggc ggg ctt tgg ctg cgg gtg gag ccc ctg aat gta agc ttg cag tga Gly Gly Leu Trp Leu Arg Val Glu Pro Leu Asn Val Ser Leu Gln * 535 540 545	1748
etttetgace catecacetg tttttttgca gattgtcatg aataaaacgg tgctgtcaaa	1808
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tgg gaa act ggg ggt ttc ctg gta act gga ctc cta gca aac tcc caa Trp Glu Thr Gly Gly Phe Leu Val Thr Gly Leu Leu Ala Asn Ser Gln gga ttc agg atg tcg ctg ctg agc ctg ccc tgg ctg ggc ctc aga ccg Gly Phe Arg Met Ser Leu Leu Ser Leu Pro Trp Leu Gly Leu Arg Pro gtg gca acg tcc cca tgg cta ctc ctg ctg ctg gtt gtg ggc tcc tgg Val Ala Thr Ser Pro Trp Leu Leu Leu Leu Val Val Gly Ser Trp cta ctc gcc cgc atc ctg gct tgg acc tat gcc ttc tat aac aac tgc 

WO	01/55	5437												r	CI/US	01/02023
Leu	Leu	Ala	Arg 55	Ile	Leu	Ala	Trp	Thr 60	Tyr	Ala	Phe	Tyr	Asn 65	Asn	Cys	
cgc Arg	cgg Arg	ctc Leu 70	cag Gln	tgt Cys	ttc Phe	cca Pro	cag Gln 75	ccc Pro	cca Pro	aaa Lys	cgg Arg	aac Asn 80	tgg Trp	ttt Phe	tgg Trp	356
ggt Gly	cac His 85	ctg Leu	ggc Gly	ctg Leu	atc Ile	act Thr 90	cct Pro	aca Thr	gag Glu	gag Glu	ggc Gly 95	ttg Leu	aag Lys	aac Asn	tcg Ser	404
acc Thr 100	cag Gln	atg Met	tcg Ser	gcc Ala	acc Thr 105	tat Tyr	tcc Ser	cag Gln	ggc Gly	ttt Phe 110	acg Thr	ata Ile	tgg Trp	ctg Leu	ggt Gly 115	452
ccc Pro	atc  Ile	atc Ile	ccc Pro	ttc Phe 120	atc Ile	gtt Val	tta Leu	tgc Cys	cac His 125	cct Pro	gac Asp	acc Thr	atc Ile	cgg Arg 130	tct Ser	· 500
atc Ile	acc Thr	aat Asn	gcc Ala 135	tca Ser	gct Ala	gcc Ala	att Ile	gca Ala 140	ccc Pro	aag Lys	gat Asp	aat Asn	ctc Leu 145	ttc Phe	atc Ile	548
agg Arg	ttc Phe	ctg Leu 150	aag Lys	ccc Pro	tgg Trp	ctg Leu	gga Gly 155	gaa Glu	Gly 999	ata Ile	ctg Leu	ctg Leu 160	agt Ser	ggc	ggt Gly	596
gac Asp	aag Lys 165	Trp	agc Ser	cgc Arg	cac His	cgt Arg 170	cgg Arg	atg Met	ctg Leu	acg Thr	pro	Ala	ttc Phe	cat His	ttc Phe	644
aac Asn 180	Ile	ctg Leu	aag Lys	tcc Ser	tat Tyr 185	Ile	acg Thr	atc Ile	ttc Phe	aac Asn 190	Lys	agt Ser	gca Ala	aac Asn	atc Ile 195	692
atg Met	ctt Leu	gac Asp	aag Lys	tgg Trp 200	Gln	cac His	ctg Leu	gcc Ala	tca Ser 205	Glu	ggc	ago Ser	agt Ser	tgt Cys 210	ctg Leu	740
gac Asp	atg Met	ttt Phe	gag Glu 215	His	ato	agc Ser	cto Lev	atg Met 220	Thr	ttg Leu	gac Asp	agt Ser	cta Leu 225	. GLn	aaa Lys	788
tgo Cys	ato Ile	tto Phe	e Ser	ttt Phe	gac Asp	ago Ser	cat His	Cys	cag Gln	gag Glu	agg Arg	9 CCC 9 Pro 240	Ser	gaa Glu	tat Tyr	836
att Ile	gcc Ala 245	Thi	c ato	ttg Lev	gag Glu	cto Leu 250	Ser	gcc Ala	ctt Leu	gta Val	gag Glu 25	ı Lys	aga Arg	ago Ser	cag Gln	884
cat His 260	: Ile	cto Lev	c cag u Glr	cac His	ato Met	: Asp	ttt Phe	ctg Lev	tat Tyr	tac Tyr 270	Le	c tco u Sei	cat His	gac Asp	999 Gly 275	932
cgg	g dgo g Arg	tte g Phe	c cad e His	agg Arg 280	g Ala	tgo Cys	cgo Arg	c cts g Lev	gtg 1 Val 289	His	gae Ası	c tto p Phe	aca Thi	gad Asp 290	gct Ala	980
gto Va:	c ato	c cg	g gag g Glv 295	ı Arg	g egt	cgc g Arg	ace Thi	c cto Leu 300	ı Pro	c act	c Car	g ggt n Gly	att / Ile 309	ASI	gat Asp	1028
tti	t tt	c aa	a gad	c aaa	a gc	aag	g to	c aag	g act	ttg	g ga	t tt	ati	gat	gtg	1076

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Phe	Phe	Lys 310	Asp	Lys	Ala	Lys	Ser 315	Lys	Thr	Leu	Asp	Phe 320	Ile	Asp	Val	
								gly aaa								1124
								atg Met								1172
								aag Lys								1220
								ggc Gly 380								1268
					•			gag Glu	_	-	_					1316
								aaa Lys								1364
								tgc Cys								1412
			_					cga Arg	_	_		_	-		-	1460
		_		_	-			aaa Lys 460				_			-	1508
			-					act Thr			_	-		-	-	1556
	_	Pro	Phe	-	Phe	Asp	Pro	gag Glu		Ser	Lys	Gly				1604
								999 999								1652
								gtg Val								1700
cac His	ttc Phe	cgg	ttc Phe 535	ctg Leu	cca Pro	gac Asp	cac His	act Thr 540	gag Glu	ccc Pro	cgc Arg	agg Arg	aag Lys 545	ctg Leu	gaa Glu	1748
			Arg					ctt Leu								1796
aat	gta	ggc	ttg	cag	tga	ctt	tct	gacc	catc	ca c	ctgt	tttt	t tg	caga	ttgt	1850

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ctg tcc tgg ctg ggc ctc ggg cag gtg gca gca ttc ccg tgg ctg ctc Leu Ser Trp Leu Gly Leu Gly Gln Val Ala Ala Phe Pro Trp Leu Leu 10 15 20	162
ctg ctg ctg gct ggg gcc tcc cgg ctc ctg gcc ggc ttc ctg gcc tgg Leu Leu Leu Ala Gly Ala Ser Arg Leu Leu Ala Gly Phe Leu Ala Trp 25 30 35	210
acc tat gcc ttc tat gac aac tgc cgc cgc ctt cag tac ttt cca caa Thr Tyr Ala Phe Tyr Asp Asn Cys Arg Arg Leu Gln Tyr Phe Pro Gln 40 45 50	258
ccc cca aaa cag aaa tgg ttt tgg ggt caa cca gga cct cct gct att Pro Pro Lys Gln Lys Trp Phe Trp Gly Gln Pro Gly Pro Pro Ala Ile 55 60 65	306
gcg ccc aag gat gat ctc tcc atc agg ttc ctg aag ccc tgg ctg gga Ala Pro Lys Asp Asp Leu Ser Ile Arg Phe Leu Lys Pro Trp Leu Gly 70 75 80 85	354
gaa ggg ata ctg ctg agt ggc ggt gac aag tgg agc cgc cac cgt cgg Glu Gly Ile Leu Leu Ser Gly Gly Asp Lys Trp Ser Arg His Arg Arg 90 95 100	402
atg ctg acg ccc gcc ttc cat ttc aac atc ctg aaa ccc tat ata aag Met Leu Thr Pro Ala Phe His Phe Asn Ile Leu Lys Pro Tyr Ile Lys 105 110 115	450
atc ttc aac agg agt gtg aac atc atg cac gac aag tgg cag cac ctg  Ile Phe Asn Arg Ser Val Asn Ile Met His Asp Lys Trp Gln His Leu  120 125 130	498
gcc tca gag ggc agc agt cgt ctg gac atg ttt gag cac atc agc ctc Ala Ser Glu Gly Ser Ser Arg Leu Asp Met Phe Glu His Ile Ser Leu 135 140 145	546
atg acc ttg gac agt ctg cag aaa tgc atc ttc agc ttt gac agc cat Met Thr Leu Asp Ser Leu Gln Lys Cys Ile Phe Ser Phe Asp Ser His 150 155 160 165	594

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						aac Asn										690

ctg tat tac ctc tcc cat gac ggg tgg cgc ttc cgc agg gcc tgc cgc 738

Leu Tyr Tyr Leu Ser His Asp Gly Trp Arg Phe Arg Arg Ala Cys Arg
200 205 210

190

ctg gtg cac gac ttc aca gat gcc gtc atc cag gag cgg cgc cat acc

786
Leu Val His Asp Phe Thr Asp Ala Val Ile Gln Glu Arg Arg His Thr

215

220

225

ctt ccc act cag ggc cat gac acc aca gcc agt ggt ctc tcc tgg gtc

Leu Pro Thr Gln Gly His Asp Thr Thr Ala Ser Gly Leu Ser Trp Val

230 245

ctg tac aac ctc gcg agg cac cca gaa tac cag gag cac tgc cgg cag

Leu Tyr Asn Leu Ala Arg His Pro Glu Tyr Gln Glu His Cys Arg Gln

250

260

gag gtg caa gag ctt ctg aag gac cgc gat cct aaa gag att gaa tgg 930 Glu Val Gln Glu Leu Leu Lys Asp Arg Asp Pro Lys Glu Ile Glu Trp 265 270 275

gac gac ctg gcc cag ctg ccc ttc ctg acc atg tgc gtg aag gag agc 978
Asp Asp Leu Ala Gln Leu Pro Phe Leu Thr Met Cys Val Lys Glu Ser
280 285 290

ctg agg tta cat ccc cca gct ccc ttc atc tcc cga tgc tgc acc cag 1026 Leu Arg Leu His Pro Pro Ala Pro Phe Ile Ser Arg Cys Cys Thr Gln 295 300 305

gac att gtt ctc cca gat ggc cga gtc atc ccc aaa ggc att acc tgc 1074 Asp Ile Val Leu Pro Asp Gly Arg Val Ile Pro Lys Gly Ile Thr Cys 310 325

ctc atc gat att ata ggg gtc cat cac aac cca act gtg tgg ccg gat 1122 Leu Ile Asp Ile Ile Gly Val His His Asn Pro Thr Val Trp Pro Asp 330 335 340

cct gag gtc tac gac ccc ttc cgc ttt gac cca gag aac agc aag ggg 1170 Pro Glu Val Tyr Asp Pro Phe Arg Phe Asp Pro Glu Asn Ser Lys Gly 345 350 355

agg tca cct ctg gct ttt att cct ttc tcc gca ggg ccc agg aac tgc 1218
Arg Ser Pro Leu Ala Phe Ile Pro Phe Ser Ala Gly Pro Arg Asn Cys
360 365 370

atc ggg cag gcg ttc gcc atg gcg gag atg aaa gtg gtc ctg gcg ttg

1266

Ile Gly Gln Ala Phe Ala Met Ala Glu Met Lys Val Val Leu Ala Leu

375

380

385

atg ctg ctg cac ttc cgg ttc ctg cca gac cac act gag ccc cgc agg

Met Leu Leu His Phe Arg Phe Leu Pro Asp His Thr Glu Pro Arg Arg

390 395 400 405

aag ctg gaa ttg atc atg cgc gcc gag ggc ggg ctt tgg ctg cgg gtg

Lys Leu Glu Leu Ile Met Arg Ala Glu Gly Gly Leu Trp Leu Arg Val

410

WO 01/55437 PC1/	US01/02623
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425 430	
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1547

800

attaaatctc ggg

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aat tag tagaagaatt aaaattcaat cctaagtctg tctgacccca aagcccatga 43 Asn *	33
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acctcaatta tctcatctat aaaaggcagc tagatcttaa ctcactgggt tctcgtgagg 24	10
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gac cac aga tcc ccg gtt gag agg aat gcc cag acc aca ctc atc cta  Asp His Arg Ser Pro Val Glu Arg Asn Ala Gln Thr Thr Leu Ile Leu  25 30 35	0 (
Cac tca tcc cta tac tca ttg tcc ctt ggg aac caa ctg cag gga gga His Ser Ser Leu Tyr Ser Leu Ser Leu Gly Asn Gln Leu Gln Gly Gly 40 45 50 55	8
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638

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gcc Ala	act Thr	ttt Phe 25	ttg Leu	aga Arg	aaa Lys	aaa Lys	tta Leu 30	agt Ser	aag Lys	gta Val	gcc Ala	ttc Phe 35	agt Ser	tgt Cys	ctt Leu	271
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gct Ala	Gly ggg	att Ile 105	aca Thr	ggt Gly	gtg Val	cac His	cac His 110	cac His	acc Thr	tat Tyr	gta Val	aat Asn 115	ttt Phe	gta Val	tgg Trp	511
aca Thr	gta Val 120	cag Gln	aag Lys	gcg Ala	gtt Val	cac His 125	tgt Cys	gtt Val	ggc Gly	cag Gln	gct Ala 130	agc Ser	tgg Trp	gaa Glu	ctc Leu	559
ctg Leu 135	Thr	tca Ser	agg Arg	gat Asp	cca Pro 140	ccc Pro	acc Thr	ttg Leu	gcc Ala	tcc Ser 145	cac His	agg Arg	gct Ala	Gly 999	att Ile 150	. 607
aca Thr	ggc Gly	atg Met	agc Ser	cac His 155	cgc Arg	acc Thr	tgg Trp	gca Ala	aaa Lys 160	gtg Val	ttc Phe	ctt Leu	aaa Lys	aga Arg 165	gtg Val	655
att Ile	ttt Phe	cta Leu	aat Asn 170	aga Arg	gaa Glu	tac Tyr	gat Asp	ttg Leu 175	act Thr	atg Met	ttt Phe	tgc Cys	ttt Phe 180	tta Leu	aaa Lys	703
tag	acat	act	catc	tctg	ac t	gtta	ttct	a ag	gatt	aagt	gct	atat	aaa	gcac	agcaaa	763
taa	ttt	gcc	agat	gcaa	ta g	aaat	tagt	t tc	ttga	ggaa	tgt	gtca	ata	tcta	gcaatt	823
tta	cata	ggc	attt	accc	tt t	gaac	caga	a ac	ttca	ctta	tag	aaat	cta	tect	aaagac	883
aca	cagt	caa	aaat	tcaa	ga c	gggc	atgg	t gg	ctca	tggc	tgc	aatc	сса	gcac	tttagg	943
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205

Leu Phe Cys Leu Asn Thr Gln His Leu Ser Val Arg Asn Asn Phe Val

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<210> 322 <211> 307 <212> PRT <213> Homo sapiens

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245 250 255 245 250 Met Phe Ala Thr Thr Leu Gly Val Met Gly Leu Trp Ser Gly Ile Ile 260 265 270 Ile Cys Thr Val Phe Gln Ala Val Cys Phe Leu Gly Phe Ile Ile Gln 275 280 285 Leu Asn Trp Lys Lys Ala Cys Gln Gln Gly Ala Leu Lys Thr Leu Lys 295 300 Glu Phe \* 305 306

<210> 323

<211> 107

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<211> 64

<212> PRT

<213> Homo sapiens

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 Ser Phe Leu Leu Gln Asn Asn Gly Met Tyr Ser Leu

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 Ser Leu Gln Leu Pro Val Leu Cys Val Leu Lys Ser Phe Lys Ala Tyr
 20
 25
 30

 Ser Leu Leu Trp Gly Val Ser Thr Gly Val Lys Glu Gly Phe Ala Gly
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 Arg Thr Ile Val Asn His Glu Ser Tyr Tyr Leu Arg Ile Val Trp \*
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<210> 321

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<212> PRT

<213> Homo sapiens

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Met Cys Thr Leu Phe Met His Leu Leu Phe Cys His Leu Gln Ser Ile

1 5 10 15

Leu Ser Gly Leu Pro Pro Pro Pro Ala Glu Pro Glu Pro Glu Pro Glu 70 75 Pro Glu Pro Glu Pro Ala Leu Asp Leu Ala Ala Leu Arg Ala Val Ala 85 90 Cys Asp Cys Leu Leu Gln Glu His Phe Tyr Leu Arg Arg Arg Arg 105 110 Val His Arg Tyr Glu Glu Ser Glu Val Ile Ser Leu Pro Phe Leu Asp 120 125 115 Gln Leu Val Ser Thr Leu Val Gly Leu Leu Ser Pro His Asn Pro Ala 130 135 140 Leu Ala Ala Ala Leu Asp Tyr Arg Cys Pro Val His Phe Tyr Trp 150 155 Val Arg Gly Glu Glu Ile Ile Pro Arg Gly His Arg Arg Gly Arg Ile 170 175 Asp Asp Leu Arg Tyr Gln Ile Asp Asp Lys Pro Asn Asn Gln Ile Arg 180 185 190 Ile Ser Lys Gln Leu Ala Glu Phe Val Pro Leu Asp Tyr Ser Val Pro 205 195 200 Ile Glu Ile Pro Thr Ile Lys Cys Lys Pro Asp Lys Leu Pro Leu Phe 215 220 Lys Arg Gln Tyr Glu Asn His Ile Phe Val Gly Ser Lys Thr Ala Asp 230 235 Pro Cys Cys Tyr Gly His Thr Gln Phe His Leu Leu Pro Asp Lys Leu 245 250 255 Arg Arg Glu Arg Leu Leu Arg Gln Asn Cys Ala Asp Gln Ile Glu Val 260 265 270 Val Phe Arg Ala Asn Ala Ile Ala Ser Leu Phe Ala Trp Thr Gly Ala 275 280 285 Gln Ala Met Tyr Gln Gly Phe Trp Ser Glu Ala Asp Val Thr Arg Pro 295 300 Phe Val Ser Gln Ala Val Ile Thr Asp Gly Lys Tyr Phe Ser Phe Phe 310 315 Cys Tyr Gln Leu Asn Thr Leu Ala Leu Thr Thr Gln Ala Asp Gln Asn 325 330 Asn Pro Arg Lys Asn Ile Cys Trp Gly Thr Gln Ser Lys Pro Leu Tyr 340 345 Glu Thr Ile Glu Asp Asn Asp Val Lys Gly Phe Asn Asp Asp Val Leu 360 365 Leu Gln Ile Val His Phe Leu Leu Asn Arg Pro Lys Glu Glu Lys Ser 370 380 Gln Leu Leu Glu Asn 385 389

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<211> 304

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<213> Homo sapiens

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<210> 316 <211> 389 <212> PRT <213> Homo sapiens

<400> 316

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 Trp

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 His
 Ala
 Ala
 Glu
 Asp
 Glu
 Lys
 Leu
 Arg
 Ile

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 Val
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 Pro
 Gln
 Thr
 Phe

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 Asp
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 Gln
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 Phe
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 Lys
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 Val
 Phe

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<210> 313 <211> 47 <212> PRT <213> Homo sapiens

<210> 314 <211> 101 <212> PRT <213> Homo sapiens

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PCT/US01/02623 WO 01/55437

<213> Homo sapiens

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<210> 308 <211> 70 <212> PRT <213> Homo sapiens

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<210> 309 <211> 150 <212> PRT

<213> Homo sapiens

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<210> 304 <211> 49 <212> PRT <213> Homo sapiens

<210> 305 <211> 107 <212> PRT <213> Homo sapiens

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<210> 306 <211> 47 <212> PRT <213> Homo sapiens

<210> 307 <211> 70 <212> PRT

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Thr Arg Val Glu Pro Pro Gln Tyr Met Ile Asp Leu Tyr Asn Arg Tyr
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                        90
Thr Ser Asp Lys Ser Thr Thr Pro Ala Ser Asn Ile Val Arg Ser Phe
         100
                  105
                                         110
Ser Met Glu Asp Ala Ile Ser Ile Thr Ala Thr Glu Asp Phe Pro Phe
   115 120
                                       125
Gln Lys His Ile Leu Leu Phe Asn Ile Ser Ile Pro Arg His Glu Gln
           135
                                   140
Ile Thr Arg Ala Glu Leu Arg Leu Tyr Val Ser Cys Gln Asn His Val
               150
                               155
Asp Pro Ser His Asp Leu Lys Gly Ser Val Val Ile Tyr Asp Val Leu
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                  170
Asp Gly Thr Asp Ala Trp Asp Ser Ala Thr Glu Thr Lys Thr Phe Leu
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Val Ser Gln Asp Ile Gln Asp Glu Gly Trp Glu Thr Leu Glu Val Ser
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Ser Ala Val Lys Arg Trp Val Arg Ser Asp Ser Thr Lys Ser Lys Asn
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                             220
Lys Leu Glu Val Thr Val Glu Ser His Arg Lys Gly Cys Asp Thr Leu
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                     235 240
Asp Ile Ser Val Pro Pro Gly Ser Arg Asn Leu Pro Phe Phe Val Val
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                             250
Phe Ser Asn Asp His Ser Ser Gly Thr Lys Glu Thr Arg Leu Glu Leu
       260
                          265
Arg Glu Met Ile Ser His Glu Gln Glu Ser Val Leu Lys Lys Leu Ser
    275
                      280
                                      285
Lys Asp Gly Ser Thr Glu Ala Gly Glu Ser Ser His Glu Glu Asp Thr
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                                  300
Asp Gly His Val Ala Ala Gly Ser Thr Leu Ala Arg Arg Lys Arg Ser
              310
                        315
Ala Gly Ala Gly Ser His Cys Gln Lys Thr Ser Leu Arg Val Asn Phe
             325
                            330
Glu Asp Ile Gly Trp Asp Ser Trp Ile Ile Ala Pro Lys Glu Tyr Glu
        340
                 345
Ala Tyr Glu Cys Lys Gly Gly Cys Phe Phe Pro Leu Ala Asp Asp Val
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            360
                               365
Thr Pro Thr Lys His Ala Ile Val Gln Thr Leu Val His Leu Lys Phe
                   375
                                  380
Pro Thr Lys Val Gly Lys Ala Cys Cys Val Pro Thr Lys Leu Ser Pro
               390
                        395 400
Ile Ser Val Leu Tyr Lys Asp Asp Met Gly Val Pro Thr Leu Lys Tyr
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His Tyr Glu Gly Met Ser Val Ala Glu Cys Gly Cys Arg *
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<210> 303 <211> 56 <212> PRT <213> Homo sapiens

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 Ile
 Ile
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 His
 Arg

 Arg
 Thr
 Val
 Leu
 Cys
 Alg
 Ser
 Gly
 Ile
 Ile
 Met
 His
 Arg

 Gly
 Lys
 Thr
 Pro
 Pro
 Leu
 Lys
 Met
 Val
 Cys
 Arg
 Phe
 Glu
 Glu
 Ser
 Phe

 Ser
 Cys
 Leu
 Phe
 Leu
 Ass
 Ser
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 50
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 55
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 Phe Ile Ile Val Thr Phe Lys Trp Ile Asp Lys Phe Ile Leu Asn Ile
 65
 70
 75
 80

 Ser Ile Leu Ile Ser Asn Thr Val Asn Val Asn Ser His Asn Pro His
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 Lys Gln Lys Phe Phe Gly Asp Leu Ser Asn Phe
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<210> 301
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<210> 302 <211> 430 <212> PRT <213> Homo sapiens

<400> 302

 Met
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 Arg
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<210> 296 <211> 38 <212> PRT <213> Homo sapiens

<210> 297 <211> 57 <212> PRT <213> Homo sapiens

<400> 297

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<210> 293 <211> 113 <212> PRT <213> Homo sapiens

<400> 293

Met Ala Tyr Ile Ile Gln Pro Ser Ser Thr Ser Val Ile Ser Val Lys 10 Leu Ser Leu Gly His Cys Ala Ser Ala Thr Leu Thr Ser Leu His Ile 20 25 Ser His Ile His Gln Ala Cys Ser Cys Leu Gly Ala Phe Val Leu Thr 35 40 Met Phe Cys Ser Glu Asn Thr Leu Pro Gln Asp Ile Leu Gln Leu Ser 55 60 Tyr Cys Ile Gln Leu Ser Ala Gln Val Leu Thr Asp Glu Thr Cys His 70 75 Pro Tyr Ser Thr Pro Cys Ser Ala Leu Leu Asn Ser Asn Cys Thr Tyr 85 90 Gly Pro Leu Asn Asn Ile His Leu Val Thr Tyr Phe Tyr Leu Ser Ala 113

<210> 294

<211> 107 <212> PRT <213> Homo sapiens

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<210> 291 <211> 96 <212> PRT <213> Homo sapiens

<400> 291 Met Leu Leu Trp Val Phe Leu Gln Leu Asn Tyr Lys Ile Gln Ala Ile 5 10 Pro Thr Tyr Glu Thr Val Met Thr Phe Phe Lys Ser Phe Pro Glu Asn 20 25 Cys Cys Phe Leu Asp Arg Asp Ile Gly Gln Ser Leu Arg Pro Leu Phe 4.5 35 40 Leu Cys Leu Arg Leu His Gly Ile Thr Lys Gly Lys Asp Leu Arg Cys 55 60 Cys Gly Thr Leu Thr Ser Ser Gln Ser His Gly Ser Thr Arg Leu Gln 75 70 Ser Thr Ile Thr Thr His Trp Arg Met Gly Ala Thr Trp Ser Thr \* 90

<210> 292 <211> 366 <212> PRT <213> Homo sapiens

<400> 292 Met Leu Tyr Trp Val Val Ile His Phe Gly Ala Arg Gly Pro Gly Gly 5 · 10 Arg Arg Lys Arg Arg Thr Thr Asn Gly Glu Gly Arg Asn Ala Ala Arg 25 20 His Ala Gly Lys Glu Gly Asn Pro Arg Lys Pro Thr Gly Asn Ala Gln 45 40 35 Thr Pro Met Asp Pro Arg Lys Arg Lys Gly Ser Leu Thr Pro Gly 60 55 Pro Asn Arg Arg Gln Glu Ser Glu Gly Ala Arg Arg Gln Ser Arg 75 70 Arg Gly Glu Asn Gly Ser Glu Ala Ala Gln Ser Pro Ser Arg Gly Thr 90

<400> 287 Met Phe Leu Arg Gly Ile Pro Ser Arg Arg Glu Ser Leu Lys Thr Asn 10 Thr His Arg Ser Trp Arg Trp Ala Pro His Ser Pro Leu Asp Leu Thr 20 25 Ile Arg Asn Leu Leu Cys His Leu Phe Ile Lys Leu Ser Gln Ala Gln 35 40 Lys Ala Cys Pro Asn His Met Leu Arg Ala Lys Gln Met Glu Gln Lys 55 60 Leu Pro Gln Ala Ala Gly Ser His Tyr Gly Trp Asp Glu Ala Arg Thr 70 75 Trp Ala His Thr Gly Cys Lys Ala Ala Asp Ala Trp Val Asp Pro Gly 85 90 Val Pro Glu Gln Asp Leu Pro Ala Phe Asn 100

<210> 288 <211> 114 <212> PRT <213> Homo sapiens

<400> 288 Met Ser Ser Trp Phe Leu Arg Ala Gly His Gly Leu Ile Trp Val Leu 10 Phe Phe Arg Ile Gly Gln Ala Ala Val Gly Val Ser Ala Gly Pro Gly 20 25 Gly Ser Pro Lys Ala His Leu Gly Arg Val Ala Ser Gln His Pro His 35 40 45 Gly Ala Glu Ser Arg Ala Cys Leu Leu Ala Arg Gly Leu Pro Lys Ala 55 60 Leu Ser Ser Met Leu Ala Val Asp Cys Arg Pro Arg Ser Gly Pro Leu 70 75 His Arg Ala Ala His Ile Met Ala Ala Ser Leu Ile Ser Lys Pro Val 85 90 Arg Gly Cys Leu Ser Glu Asp Asp Ile Pro Ser Pro Leu Ser Asp Ser 105 Ala Tyr 114

<210> 289 <211> 52 <212> PRT <213> Homo sapiens

<210> 290

<210> 285
<211> 48
<212> PRT
<213> Homo sapiens

<210> 286 <211> 183 <212> PRT <213> Homo sapiens

<400> 286 Met Asn Ser Asn Leu Pro Ala Glu Asn Leu Ser Ile Ala Val Asn Met 5 10 Thr Lys Thr Leu Pro Thr Ala Val Thr His Gly Phe Asn Ser Thr Asn 20 25 Asp Pro Pro Ser Met Ser Ile Thr Arg Leu Phe Ser Ala Leu Leu Glu 40 Cys Phe Gly Ile Val Leu Cys Gly Tyr Ile Ala Gly Arg Ala Asn Val 55 60 Ile Thr Ser Thr Gln Ala Lys Gly Leu Gly Asn Phe Val Ser Arg Phe 65 70 75 Ala Leu Pro Ala Leu Leu Phe Lys Asn Met Val Val Leu Asn Phe Ser 85 90 Asn Val Asp Trp Ala Phe Leu Tyr Ser Ile Leu Ile Ala Lys Ala Ser 100 105 110 Val Phe Phe Ile Val Cys Val Leu Thr Leu Leu Val Ala Ser Pro Asp 120 Ser Arg Phe Ser Lys Ala Gly Leu Phe Pro Ile Phe Ala Thr Gln Ser 135 140 Asn Asp Phe Ala Leu Gly Tyr Pro Ile Gly Lys Leu Ile Phe Ile Phe 145 150 155 160 Gln Val Phe Lys Lys Phe Asn Phe Asn Leu Phe Arg His Leu Leu Val 165 170 Thr Asp Ser Tyr Ser His Ile

<210> 287 <211> 106 <212> PRT <213> Homo sapiens

180

183

<210> 284 <211> 474 <212> PRT <213> Homo sapiens

<400> 284 Met Gly Ser Thr Ala Ile Leu Ala Leu Leu Leu Ala Val Leu Gln Gly 10 Val Cys Ala Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys 20 25 Pro Gly Glu Ser Val Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe 35 40 Ser Asp Tyr Trp Val Ala Trp Val Arg Gln Ser Pro Asp Lys Gly Leu 55 Ala Trp Met Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser 70 75 Pro Ser Phe Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser 85 90 Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Asp Ser Asp Thr Ala Met 100 105 110 Tyr Tyr Cys Ala Arg Gly Ala Arg Gly Thr Ala Pro Ser Tyr His Tyr 115 120 Tyr Gly Leu Asp Val Trp Gly Arg Gly Thr Ser Val Thr Val Ser Ser 135 140 Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys 150 155 160 Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr 170 165 175 Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser 180 185 Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser 195 200 205 Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr 215 Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys 230 235 Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys 245 250 Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro 260 265 270 Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys 275 280 285 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp 290 295 300 Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu 310 315 Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu 325 330 His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn 340 345 Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly 355 360 Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu 375 380 Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr 390 395 Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn 405 410 Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe 420 425

<210> 282 <211> 113 <212> PRT <213> Homo sapiens

<400> 282 Met Cys His Trp Gln Asn Ser Phe Leu Cys Gln Ser Phe Leu Thr Phe 10 Gly Ser Ile Leu Ala Leu Leu Ala Gly Lys Ala Cys Tyr Pro Glu Ser 20 25 Glu Ser Ile Arg Glu Leu Phe Met Trp Ser Leu Glu Leu Tyr Ser Leu 40 35 Pro Phe Tyr Leu Phe Phe Lys Leu Ser Pro Leu Asn Leu Pro Gly Lys 50 60 Leu Gly Leu Ile Glu Thr Leu Ser Thr Cys Leu Gly Gln Lys Leu Asp 70 75 80 Pro Val Leu Glu Thr Leu Gln Arg Val Arg Ser Met Ala Ser Leu Ile 90 Ala Asn Phe Phe Val Pro Phe Ile Gln Lys Lys Gly Gln Leu Ile Thr 105

<210> 283 <211> 231 <212> PRT

<213> Homo sapiens

<400> 283 Met Ala Trp Ile Pro Leu Phe Leu Gly Val Leu Ala Tyr Cys Thr Gly 10 Ser Val Ala Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser 20 25 Pro Gly Lys Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Leu Gly Asp 35 40 Lys Tyr Ala Ser Trp Tyr Gln Gln Lys Ala Gly Gln Ser Pro Val Leu 50 55 60 Val Ile Tyr Arg His Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe 65 70 75 80 Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr 85 90 95 Gln Val Met Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser 105 Ile Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro 120 125 115 Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu 135 140 Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro 150 155 160 Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala 165 170 175 Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala 180 185 . 190 Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg 200 205 Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr 215 Val Ala Pro Thr Glu Cys Ser 230 231

Gly Ser Ser Ser Leu Ser Leu Thr Arg Lys Asn Ser Pro Lys Ser Gly Ser Pro Lys Ser Ser Ser Leu Leu Lys Leu Lys Ala Glu Lys Asn Ala Gln Ala Glu Met Gly Lys Asn His Ser Ser Ala Ser Phe Ser Ser Ser Ile Thr Ile Asn Thr Thr Cys Cys Ser Ser Ser Ser Ser Ser Ser Ser Leu Ser Lys Thr Ser Gly Asp Leu Lys Pro Arg Ser Ala Ser Asp Ala Gly Ile Arg Gly Thr Pro Lys Val Arg Ala Lys Lys Asp Ala Asp 565 570 Ala Asn Ala Gly Leu Thr Ser Cys Pro Arg Ala Lys Pro Ser Val Arg Pro Lys Pro Phe Leu Asn Arg Ala Glu Ser Gln Ser Gln Glu Lys Met Asp Ile Ser Thr Leu Arg Arg Gln Leu Arg Pro Thr Gly Gln Leu Arg Gly Gly Leu Lys Gly Ser Lys Ser Glu Asp Ser Glu Leu Pro Pro Gln Thr Ala Ser Glu Ala Pro Ser Glu Gly Ser Arg Arg Ser Ser Ser Asp Leu Ile Thr Leu Pro Ala Thr Thr Pro Pro Cys Pro Thr Lys Lys Glu Trp Glu Gly Pro Ala Thr Ser Tyr Met Thr Cys Ser Ala Tyr Gln Lys Val Gln Asp Ser Glu Ile Ser Phe Pro Ala Gly Val Glu Val Gln Val Leu Glu Lys Gln Glu Ser Gly Trp Trp Tyr Val Arg Phe Gly Glu Leu Glu Gly Trp Ala Pro Ser His Tyr Leu Val Leu Asp Glu Asn Glu Gln 725 730 Pro Asp Pro Ser Gly Lys Glu Leu Asp Thr Val Pro Ala Lys Gly Arg Gln Asn Glu Gly Lys Ser Asp Ser Leu Glu Lys Ile Glu Arg Arg Val Gln Ala Leu Asn Thr Val Asn Gln Ser Lys Lys Ala Thr Pro Pro Ile Pro Ser Lys Pro Pro Gly Gly Phe Gly Lys Thr Ser Gly Thr Pro Ala Val Lys Met Arg Asn Gly Val Arg Gln Val Ala Val Arg Pro Gln Ser Val Phe Val Ser Pro Pro Pro Lys Asp Asn Asn Leu Ser Cys Ala Leu Arg Arg Asn Glu Ser Leu Thr Ala Thr Asp Gly Leu Arg Gly Val Arg Arg Asn Ser Ser Phe Ser Thr Ala Arg Ser Ala Ala Ala Glu Ala Lys Gly Arg Leu Ala Glu Arg Ala Ala Ser Gln Gly Ser Asp Ser Pro Leu Leu Pro Ala Gln Arg Asn Ser Ile Pro Val Ser Pro Val Arg Pro Lys Pro Ile Glu Lys Ser Gln Phe Ile His Asn Asn Leu Lys Asp Val Tyr Val Ser Ile Ala Asp Tyr Glu Gly Asp Glu Glu Thr Ala Gly Phe Gln Glu Gly Val Ser Met Glu Val Leu Glu Arg Asn Pro Asn Gly Trp Trp Tyr Cys Gln Ile Leu Asp Gly Val Lys Pro Phe Lys Gly Trp Val Pro Ser Asn Tyr Leu Glu Lys Lys Asn \* 

<213> Homo sapiens

<400> 281 Met Ile Leu Glu Gln Tyr Val Val Val Ser Asn Tyr Lys Lys Gln Glu 5 10 Asn Ser Glu Leu Ser Leu Gln Ala Gly Glu Val Val Asp Val Ile Glu 20 25 Lys Asn Glu Ser Gly Trp Trp Phe Val Ser Thr Ser Glu Glu Gln Gly 40 Trp Val Pro Ala Thr Tyr Leu Glu Ala Gln Asn Gly Thr Arg Asp Asp 55 Ser Asp Ile Asn Thr Ser Lys Thr Gly Glu Val Ser Lys Arg Arg Lys 70 75 Ala His Leu Arg Arg Leu Asp Arg Arg Trp Thr Leu Gly Gly Met Val 90 85 Asn Arg Gln His Ser Arg Glu Glu Lys Tyr Val Thr Val Gln Pro Tyr 110 105 100 Thr Ser Gln Ser Lys Asp Glu Ile Gly Phe Glu Lys Gly Val Thr Val 120 125 115 Glu Val Ile Arg Lys Asn Leu Glu Gly Trp Trp Tyr Ile Arg Tyr Leu 135 140 Gly Lys Glu Gly Trp Ala Pro Ala Ser Tyr Leu Lys Lys Ala Lys Asp . 150 155 Asp Leu Pro Thr Arg Lys Lys Asn Leu Ala Gly Pro Val Glu Ile Ile 165 170 Gly Asn Ile Met Glu Ile Ser Asn Leu Leu Asn Lys Lys Ala Ser Gly 180 185 Asp Lys Glu Thr Pro Pro Ala Glu Gly Glu Gly His Glu Ala Pro Ile 195 200 Ala Lys Lys Glu Ile Ser Leu Pro Ile Leu Cys Asn Ala Ser Asn Gly 220 215 Ser Ala Val Gly Val Pro Asp Arg Thr Val Ser Arg Leu Ala Gln Gly 230 235 Ser Pro Ala Val Ala Arg Ile Ala Pro Gln Arg Ala Gln Ile Ser Ser 245 250 255 Pro Asn Leu Arg Thr Arg Pro Pro Pro Arg Arg Glu Ser Ser Leu Gly 265 270 Phe Gln Leu Pro Lys Pro Pro Glu Pro Pro Ser Val Glu Val Glu Tyr 280 Tyr Thr Ile Ala Glu Phe Gln Ser Cys Ile Ser Asp Gly Ile Ser Phe 295 300 Arg Gly Gly Gln Lys Ala Glu Val Ile Asp Lys Asn Ser Gly Gly Trp 310 315 320 Trp Tyr Val Gln Ile Gly Glu Lys Glu Gly Trp Ala Pro Ala Ser Tyr 325 330 335 Ile Asp Lys Arg Lys Lys Pro Asn Leu Ser Arg Arg Thr Ser Thr Leu 340 345 350 Thr Arg Pro Lys Val Pro Pro Pro Ala Pro Pro Ser Lys Pro Lys Glu 355 360 365 Ala Glu Glu Gly Pro Thr Gly Ala Ser Glu Ser Gln Asp Ser Pro Arg 375 380 Lys Leu Lys Tyr Glu Glu Pro Glu Tyr Asp Ile Pro Ala Phe Gly Phe 390 395 ` Asp Ser Glu Pro Glu Leu Ser Glu Glu Pro Val Glu Asp Arg Ala Ser 410 405 415 Gly Glu Arg Arg Pro Ala Gln Pro His Arg Pro Ser Pro Ala Ser Ser 420 425 Leu Gln Arg Ala Arg Phe Lys Val Gly Glu Ser Ser Glu Asp Val Ala 435 440 445 Leu Glu Glu Glu Thr Ile Tyr Glu Asn Glu Gly Phe Arg Pro Tyr Ala 455 460 Glu Asp Thr Leu Ser Ala Arg Gly Ser Ser Gly Asp Ser Asp Ser Pro 470 475

<210> 280 <211> 301 <212> PRT <213> Homo sapiens

<400> 280 Met Phe Ser His Leu Pro Phe Asp Cys Val Leu Leu Leu Leu Leu Leu 1 5 10 Leu Leu Thr Arg Ser Ser Glu Val Glu Tyr Arg Ala Glu Val Gly Gln 20 25 Asn Ala Tyr Leu Pro Cys Phe Tyr Thr Pro Ala Ala Pro Gly Asn Leu 40 35 45 Val Pro Val Cys Trp Gly Lys Gly Ala Cys Pro Val Phe Glu Cys Gly 55 60 Asn Val Val Leu Arg Thr Asp Glu Arg Asp Val Asn Tyr Trp Thr Ser 70 75 Arg Tyr Trp Leu Asn Gly Asp Phe Arg Lys Gly Asp Val Ser Leu Thr 85 90 95 Ile Gly Asn Val Thr Leu Ala Asp Ser Gly Ile Tyr Cys Cys Arg Ile 100 105 Gln Ile Pro Gly Ile Met Asn Asp Glu Lys Phe Asn Leu Lys Leu Val 115 120 125 Ile Lys Pro Ala Lys Val Thr Pro Ala Pro Thr Leu Gln Arg Asp Phe 130 135 140 Thr Ala Ala Phe Pro Arg Met Leu Thr Thr Arg Gly His Gly Pro Ala 145 150 155 160 Glu Thr Gln Thr Leu Gly Ser Leu Pro Asp Ile Asn Leu Thr Gln Ile 165 170 175 Ser Thr Leu Ala Asn Glu Leu Arg Asp Ser Arg Leu Ala Asn Asp Leu 180 185 Arg Asp Ser Gly Ala Thr Ile Arg Ile Gly Ile Tyr Ile Gly Ala Gly 195 200 Ile Cys Ala Gly Leu Ala Leu Ala Leu Ile Phe Gly Ala Leu Ile Phe 210 215 220 Lys Trp Tyr Ser His Ser Lys Glu Lys Ile Gln Asn Leu Ser Leu Ile 230 235 240 Ser Leu Ala Asn Leu Pro Pro Ser Gly Leu Ala Asn Ala Val Ala Glu 245 250 255 Gly Ile Arg Ser Glu Glu Asn Ile Tyr Thr Ile Glu Glu Asn Val Tyr 260 265 Glu Val Glu Glu Pro Asn Glu Tyr Tyr Cys Tyr Val Ser Ser Arg Gln 275 280 285 Gln Pro Ser Gln Pro Leu Gly Cys Arg Phe Ala Met Pro 295 300 301

<210> 281 <211> 969 <212> PRT

<213> Homo sapiens

<400> 278 Met Glu Ser Ser Cys Leu Asp Ile Gly Ser Val Pro Met Gly Thr Ser 10 Cys Leu Asp Ser Trp Pro Val His Ile Ile Ser Cys Leu Asp Ser Gly 20 25 Ser Val Arg Ile Lys Thr Ser Cys Leu Asp Ser Gly Pro Val Tyr Met 35 40 Gly Thr Ser Cys Leu Asp Ser Gly Pro Val Tyr Met Gly Thr Ser Cys 55 Leu Gly Ser Glu Pro Val Tyr Met Gly Thr Ser Cys Leu Gly Ser Glu 70 75 Ser Val His Met Gly Thr Ser Cys Leu Gly Ser Glu Ser Val His Met 85 90 Gly Thr Ser Cys Leu Ala Ser Gly Pro Val His Met Gly Thr Ser Cys 100 105 110Leu Gly Ser Gly Pro Val His Met Gly Thr Ser Cys Leu Gly Ser Gly 115 120 125 Ser Glu His Met Gly Thr Ser Arg Leu Asp Ser Gly Pro Val His Val 130 135 140 Gly Thr Ser Cys Leu Gly Ser Gly Ser Glu His Val Gly Thr Ser Cys 150 155 Leu Gly Ser Glu Tyr Val Tyr Thr Gly Thr Ser Arg Leu Asp Ser Gly 165 170 175 Pro Val His Met Gly Thr Ser Cys Leu Asp Ser Ala Ser Glu His Met 180 185 Gly Thr Ser Ser Leu Asp Ser Ala Ser Glu Leu Val Asp Ile Thr Cys 195 200 205 Leu Ser Lys Val Ile Thr Pro Leu Gly Phe Trp Lys Asn His Gly Asp 210 215 220 Phe Cys Pro Gly Lys Arg Tyr Asp Ala Ile Pro Leu 230 235 236

<210> 279 <211> 224 <212> PRT <213> Homo sapiens

<400> 279

Met Glu Ser Ser Cys Leu Asp Ile Gly Ser Val His Met Gly Thr Ser 1 5 10 15 Cys Leu Asp Ser Trp Pro Val His Ile Ile Ser Cys Leu Asp Ser Gly 20 25 Ser Val Arg Ile Lys Thr Ser Cys Leu Asp Ser Gly Pro Val Tyr Met 35 40 Gly Thr Ser Cys Leu Asp Ser Gly Pro Val Tyr Met Gly Thr Ser Cys 55 Leu Gly Ser Glu Pro Val Tyr Met Gly Thr Ser Cys Leu Gly Ser Glu 75 Ser Val Tyr Met Gly Thr Ser Cys Leu Gly Ser Glu Ser Val Tyr Met 85 90 95 Gly Thr Ser Cys Leu Ala Ser Gly Pro Val His Met Gly Thr Ser Cys 105 Leu Gly Ser Gly Ser Glu His Met Gly Thr Ser Arg Leu Asp Ser Gly 115 120 125 Pro Val His Val Gly Thr Ser Cys Leu Gly Ser Gly Ser Glu His Met 130 135 140 Gly Thr Ser Cys Leu Gly Ser Glu Ser Val Tyr Thr Gly Thr Ser Arg

Gly Tyr Gly Thr Pro Met Thr Ser Asn Ala Val Arg Met Glu Ala Val 180 185 190 Glu Arg Asn Val Gly Val Ile Val Ala Ala Val Leu Val Thr Leu Ile 195 200 205 Leu Leu Gly Ile Leu Val Phe Gly Ile Trp Phe Ala Tyr Ser Arg Gly 215 220 His Phe Asp Arg Thr Lys Lys Gly Thr Ser Ser Lys Lys Val Ile Tyr . 230 235 Ser Gln Pro Ser Ala Arg Ser Glu Gly Glu Phe Lys Gln Thr Ser Ser 250 Phe Leu Val 259

<210> 277 <211> 273 <212> PRT <213> Homo sapiens

<400> 277

Met Met Ile His Gly Phe Gln Ser Ser His Arg Asp Phe Cys Phe Gly 10 Pro Trp Lys Leu Thr Ala Ser Lys Thr His Ile Met Lys Ser Ala Asp Val Glu Lys Leu Ala Asp Glu Leu His Met Pro Ser Leu Pro Glu Met 35 40 45 Met Phe Gly Asp Asn Val Leu Arg Ile Gln His Gly Ser Gly Phe Gly 55 60 Ile Glu Phe Asn Ala Thr Asp Ala Leu Arg Cys Val Asn Asn Tyr Gln 70 75 Gly Met Leu Lys Val Ala Cys Ala Glu Glu Trp Gln Glu Ser Arg Thr 85 90 Glu Gly Glu His Ser Lys Glu Val Ile Lys Pro Tyr Asp Trp Thr Tyr 105 100 Thr Thr Asp Tyr Lys Gly Thr Leu Leu Gly Glu Ser Leu Lys Leu Lys 120 Val Val Pro Thr Thr Asp His Ile Asp Thr Glu Lys Leu Lys Ala Arg 135 140 Glu Gln Ile Lys Phe Phe Glu Glu Val Leu Leu Phe Glu Asp Glu Leu 150 155 His Asp His Gly Val Ser Ser Leu Ser Val Lys Ile Arg Val Met Pro 165 170 175 Ser Ser Phe Phe Leu Leu Leu Arg Phe Phe Leu Arg Ile Asp Gly Val 180 185 Leu Ile Arg Met Asn Asp Thr Arg Leu Tyr His Glu Ala Asp Lys Thr 200 205 Tyr Met Leu Arg Glu Tyr Thr Ser Arg Glu Ser Lys Ile Ser Ser Leu 215 220 Met His Val Pro Pro Ser Leu Phe Thr Glu Pro Asn Glu Ile Ser Gln 230 235 Tyr Leu Pro Ile Lys Glu Ala Val Cys Glu Lys Leu Ile Phe Pro Glu 245 250 Arg Ile Asp Pro Asn Pro Ala Asp Ser Gln Lys Ser Thr Gln Val Glu 265 270 272

387

<210> 278 <211> 236

Ser Cys Ala Tyr Ser Gly Phe Ser Ser Pro Arg Val Glu Trp Lys Phe 55 Asp Gln Gly Asp Thr Thr Arg Leu Val Cys Tyr Asn Asn Lys Ile Thr Ala Ser Tyr Glu Asp Arg Val Thr Phe Leu Pro Thr Gly Ile Thr Phe 85 90 Lys Ser Val Thr Arg Glu Asp Thr Gly Thr Tyr Thr Cys Met Val Ser 100 105 110 Glu Glu Gly Gly Asn Ser Tyr Gly Glu Val Lys Val Lys Leu Ile Val 125 115 120 Leu Val Pro Pro Ser Lys Pro Thr Val Asn Ile Pro Ser Ser Ala Thr 140 135 Ile Gly Asn Arg Ala Val Leu Thr Cys Ser Glu Gln Asp Gly Ser Pro 150 155 Pro Ser Glu Tyr Thr Trp Phe Lys Asp Gly Ile Val Met Pro Thr Asn 170 165 Pro Lys Ser Thr Arg Ala Phe Ser Asn Ser Ser Tyr Val Leu Asn Pro 190 185 180 Thr Thr Gly Glu Leu Val Phe Asp Pro Leu Ser Ala Ser Asp Thr Gly 195 200 205 Glu Tyr Ser Cys Glu Ala Arg Asn Gly Tyr Gly Thr Pro Met Thr Ser 215 220 Asn Ala Val Arg Met Glu Ala Val Glu Arg Asn Val Gly Val Ile Val 230 235 Ala Ala Val Leu Val Thr Leu Ile Leu Leu Gly Ile Leu Val Phe Gly 245 250 Ile Trp Phe Ala Tyr Ser Arg Gly His Phe Asp Arg Thr Lys Lys Gly 260 265 Thr Ser Ser Lys Lys Val Ile Tyr Ser Gln Pro Ser Ala Arg Ser Glu 275 280 Gly Glu Phe Lys Gln Thr Ser Ser Phe Leu Val 295

<210> 276 <211> 259 <212> PRT <213> Homo sapiens

<400> 276 t Gly Thr Lys Ala Gln \

Met Gly Thr Lys Ala Gln Val Glu Arg Lys Leu Leu Cys Leu Phe Ile 10 Leu Ala Ile Leu Pro Glu Asn Asn Pro Val Lys Leu Ser Cys Ala Tyr 25 Ser Gly Phe Ser Ser Pro Arg Ala Ala Ser Tyr Glu Asp Arg Val Thr 40 Phe Leu Pro Thr Gly Ile Thr Phe Lys Ser Val Thr Arg Glu Asp Thr 60 Gly Thr Tyr Thr Cys Met Val Phe Glu Glu Gly Gly Asn Ser Tyr Gly 65 70 75 Glu Val Lys Val Lys Leu Ile Val Leu Val Pro Pro Ser Lys Pro Thr 90 85 Val Asn Ile Pro Ser Ser Ala Thr Ile Gly Asn Arg Ala Val Leu Thr 100 105 110 Cys Ser Glu Gln Asp Gly Ser Pro Pro Ser Glu Tyr Thr Trp Phe Lys 115 120 125 Asp Gly Ile Val Met Pro Thr Asn Pro Lys Ser Thr Arg Ala Phe Ser 140 135 Asn Ser Ser Tyr Val Leu Asn Pro Thr Thr Gly Glu Leu Val Phe Asp 150 155 Pro Leu Ser Ala Ser Asp Thr Gly Glu Tyr Ser Cys Glu Ala Arg Asn 170 165

Asp Asp Pro Thr Leu Ala Ile Ala Leu Ala Ala Asn Ala Trp Ala Phe 325 330 Val Leu Phe Tyr Val Ile Pro Glu Val Ser Gln Val Thr Lys Ser Ser 340 345 350 Pro Glu Gln Ser Tyr Gln Gly Asp Met Tyr Pro Thr Arg Gly Val Gly 360 Tyr Glu Thr Ile Leu Lys Glu Gln Lys Gly Gln Ser Met Phe Val Glu 375 380 Asn Lys Ala Phe Ser Met Asp Glu Pro Val Ala Ala Lys Arg Pro Val 395 390 Ser Pro Tyr Ser Gly Tyr Asn Gly Gln Leu Leu Thr Ser Val Tyr Gln 410 405 415 Pro Thr Glu Met Ala Leu Met His Lys Val Pro Ser Glu Gly Ala Tyr 420 425 430 Asp Ile Ile Leu Pro Arg Ala Thr Ala Asn Ser Gln Val Met Gly Ser 440 Ala Asn Ser Thr Leu Arg Ala Glu Asp Met Tyr Ser Ala Gln Ser His 455 460 Gln Ala Ala Thr Pro Pro Lys Asp Gly Lys Asn Ser Gln Val Phe Arg 465 470 475 Asn Pro Tyr Val Trp Asp 485 486

<210> 274 <211> 118 <212> PRT <213> Homo sapiens

<400> 274

Met Val Lys Thr Asp Ala His Leu Lys Asn Pro Pro Phe Ala Pro Phe Arg Val Tyr Thr Leu Thr Leu Ser Leu Leu Leu Lys Leu Ser His Tyr 25 Ser Cys Leu Trp Val Lys Lys Asp Phe Lys Asp Ser Ser Phe Tyr Asn 45 40 Ser Asn Asn Asn Ser Asn Ser Asn His Cys Lys Ser Leu Leu Ser Thr 55 60 His Tyr Met Pro Gly Ala Val Ile Ser Asn Leu Cys Leu Ile Ser Cys 70 75 Lys Val Ser Ser Pro Ile Lys Gln Thr His Gly Ile Ser Met Leu 85 90 Gln Met Lys Arg Leu Lys His Thr Leu Ala Arg Leu Ala Pro Gly Thr 100 His Gly Gly Ser Gln Asn 115 118

<210> 275 <211> 299 <212> PRT <213> Homo sapiens

<400> 275

 Met Gly Thr Lys Ala Gln Val Glu Arg Lys Leu Leu Cys Leu Phe Ile

 1
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 10
 15

 Leu Ala Ile Leu Leu Cys Ser Leu Ala Leu Gly Ser Val Thr Val His
 20
 25
 30

 Ser Ser Glu Pro Glu Val Arg Ile Pro Glu Asn Asn Pro Val Lys Leu
 35
 40
 45

<210> 273 <211> 486 <212> PRT <213> Homo sapiens

<400> 273

Met Arg Gly Arg Gly Ser Gln Gln Gln Gln Pro Thr Arg Arg Gln Gly
1 10 15 Gln Lys Leu Pro Ser Pro Ser Pro Ala Gly Lys Tyr Glu Ser Ala Gln 25 Pro Gly Gly Thr Gln Pro Glu Pro Gly Leu Gly Ala Arg Met Ala Ile 40 His Lys Ala Leu Val Met Cys Leu Gly Leu Pro Leu Phe Leu Phe Pro 55 60 Gly Ala Trp Ala Gln Gly His Val Pro Pro Gly Cys Ser Gln Gly Leu 75 70 Asn Pro Leu Tyr Tyr Asn Leu Cys Asp Arg Ser Gly Ala Trp Gly Ile 85 90 95 Val Leu Glu Ala Val Ala Gly Ala Gly Ile Val Thr Thr Phe Val Leu 100 105 110 Thr Ile Ile Leu Val Ala Ser Leu Pro Phe Val Gln Asp Thr Lys Lys 115 120 125 Arg Ser Leu Leu Gly Thr Gln Val Phe Phe Leu Leu Gly Thr Leu Gly 135 140 Leu Phe Cys Leu Val Phe Ala Cys Val Val Lys Pro Asp Phe Ser Thr 150 155 Cys Ala Ser Arg Arg Phe Leu Phe Gly Val Leu Phe Ala Ile Cys Phe 165 170 175 Ser Cys Leu Ala Ala His Val Phe Ala Leu Asn Phe Leu Ala Arg Lys 180 185 190 Asn His Gly Pro Arg Gly Trp Val Ile Phe Thr Val Ala Leu Leu Leu 195 200 205 Thr Leu Val Glu Val Ile Ile Asn Thr Glu Trp Leu Ile Ile Thr Leu 215 220 Val Arg Gly Ser Gly Glu Gly Gly Pro Gln Gly Asn Ser Ser Ala Gly 230 235 Trp Ala Val Ala Ser Pro Cys Ala Ile Ala Asn Met Asp Phe Val Met 245 250 255 Ala Leu Ile Tyr Val Met Leu Leu Leu Leu Gly Ala Phe Leu Gly Ala 260 265 270 Trp Pro Ala Leu Cys Gly Arg Tyr Lys Arg Trp Arg Lys His Gly Val 275 280 285 Phe Val Leu Leu Thr Thr Ala Thr Ser Val Ala Ile Trp Val Val Trp 295 300 Ile Val Met Tyr Thr Tyr Gly Asn Lys Gln His Asn Ser Pro Thr Trp 310 315

Ile Gln Glu Ala Arg Ala Asp Leu Ala Arg Arg Gly Leu Arg Phe \* 115 120 125 127

<210> 270 <211> 132 <212> PRT <213> Homo sapiens

<400> 270 Met Lys Phe Arg Ile Val Thr Cys Gln Ser Asp Trp Arg Glu Leu Trp 10 1 Val Asp Asp Ala Ile Trp Arg Leu Leu Phe Ser Met Ile Leu Phe Val \_ 25 20 Ile Met Val Leu Trp Arg Pro Ser Ala Asn Asn Gln Arg Phe Ala Phe 45 40 Ser Pro Leu Ser Glu Glu Glu Glu Glu Asp Glu Gln Lys Glu Pro Met 50 55 60 Leu Lys Glu Ser Phe Glu Gly Met Lys Met Arg Ser Thr Lys Gln Glu 65 70 75 Pro Asn Gly Asn Ser Lys Val Asn Lys Ala Gln Glu Asp Asp Leu Lys 85 90 Trp Val Glu Glu Asn Val Pro Ser Ser Val Thr Asp Val Ala Leu Pro 100 105 110 Ala Leu Leu Asp Ser Asp Glu Glu Arg Met Ile Thr His Phe Glu Arg 120 115 Ser Lys Met Glu 130 132

<210> 271 <211> 118 <212> PRT <213> Homo sapiens

<400> 271 Met Lys Thr Leu Phe Leu Asn Thr Glu Tyr Leu Met Pro Phe Leu Leu 1 5 10 Asn Gln Gly Gly Ser Leu Leu Tyr Tyr Leu Thr Leu Ala Ser Thr Asp 25 20 Leu Thr Leu Ala Val Pro Ile Cys Asn Ser Leu Ala Ile Ile Phe Thr 35 40 45 Leu Tle Val Gly Lys Ala Leu Gly Glu Asp Ile Gly Gly Lys Arg Ala ·50 55 60 Val Ala Gly Met Val Leu Thr Val Ile Gly Ile Ser Leu Cys Ile Thr 70 75 Ser Ser Val Pro Trp Thr Ala Glu Leu Gln Leu His Gly Lys Gly Gln 90 Leu Gln Thr Leu Ser Gln Lys Cys Lys Arg Glu Ala Ser Gly Thr Gln 100 105 Ser Glu Arg Phe Gly \* 115 117

<210> 272 <211> 94 <212> PRT <213> Homo sapiens

Gly Ile Arg Leu His Cys Ala Arg Gly Asn Val Leu Gly Asn Thr His 85 90 Val Val Glu Ser Gln Ser Gly Ser Trp Gly Glu Trp Ser Glu Pro Leu 105 Trp Cys Arg Gly Gly Ala Tyr Leu Val Ala Phe Ser Leu Arg Val Glu 125 120 115 Ala Pro Thr Thr Leu Gly Asp Asn Thr Ala Ala Asn Asn Val Arg Phe 130 135 140 Arg Cys Ser Asp Gly Glu Glu Leu Gln Gly Pro Gly Leu Ser Trp Gly 150 155 Asp Phe Gly Asp Trp Ser Asp His Cys Pro Lys Gly Ala Cys Gly Leu 170 175 Gln Thr Lys Ile Gln Gly Pro Arg Gly Leu Gly Asp Asp Thr Ala Leu 185 180 Asn Asp Ala Arg Leu Phe Cys Cys Arg Ser 202 200 .. 195

<210> 268 <211> 112 <212> PRT <213> Homo sapiens

<400> 268 Met Arg Gln Val Ala Arg Val Ile Val Phe Leu Thr Leu Ser Thr Leu 10 15 Ser Leu Ala Lys Thr Thr Gln Pro Ile Ser Met Asp Ser Tyr Glu Gly 25 30 20 Gln Glu Val Asn Ile Thr Cys Ser His Asn Asn Ile Ala Thr Asn Asp 45 40 35 Tyr Ile Thr Trp Tyr Gln Gln Phe Pro Ser Gln Gly Pro Arg Phe Ile 60 55 Ile Gln Gly Tyr Lys Thr Lys Val Thr Asn Glu Val Ala Ser Leu Phe 75 70 Ile Pro Ala Asp Arg Lys Ser Ser Thr Leu Ser Leu Pro Arg Val Ser 85 90 Leu Ser Asp Thr Ala Val Tyr Tyr Cys Leu Val Gly Asp Thr Gln \* 105 100

<210> 269 <211> 128 <212> PRT <213> Homo sapiens

<400> 269 Met Met Lys Ile Pro His Gln Thr Gln Lys Lys Arg Ser Leu Glu Asp 10 Pro Asn Ser Arg Pro Arg Arg Pro Arg Gly Glu Gly Glu Thr Trp Gly 30 20 25 Arg Val Thr Met Thr Lys Leu Ala Gln Trp Leu Trp Gly Leu Ala Ile 40 45 Leu Gly Ser Thr Trp Val Ala Leu Thr Thr Gly Ala Leu Gly Leu Glu 55 Leu Pro Leu Ser Cys Gln Glu Val Leu Trp Pro Leu Pro Ala Tyr Leu 70 75 Leu Val Ser Ala Gly Cys Tyr Ala Leu Gly Thr Val Gly Tyr Arg Val 90 85 Ala Thr Phe His Asp Cys Glu Asp Ala Ala Arg Glu Leu Gln Ser Gln 105

<210> 265 <211> 71 <212> PRT <213> Homo sapiens

<400> 265

<210> 266 <211> 53 <212> PRT <213> Homo sapiens

<400> 266

 Met Phe Thr His Trp Leu Gly Pro Pro Val Tyr Ile Lys Gln Phe Ile
 1
 15

 Val Met Ile Val Ser Ile Leu Thr Leu Phe Pro Val Leu Gln Gly Met
 20
 25
 30

 Leu Arg Asn Phe Leu Tyr Leu Asn Ile Met Phe Val Val Ala Leu Leu
 35
 40
 45

 Lys Ala Ile Leu \*
 50
 52
 50
 52

<210> 267 <211> 203 <212> PRT <213> Homo sapiens

<400> 267

<210> 262 <211> 65 <212> PRT <213> Homo sapiens

<210> 263 <211> 71 <212> PRT <213> Homo sapiens

<210> 264 <211> 75 <212> PRT <213> Homo sapiens

<400> 264
Met Arg Gln Ile Ala Val Phe Gln Arg Phe Met Phe Pro Phe Leu Leu
1 5 10 15
Pro Trp Leu Ser Cys Ile Phe Ser Ser Ser Gln Asn Ser Ile Tyr Tyr
20 25 30

<210> 259 <211> 65 <212> PRT <213> Homo sapiens

<400> 259

 Met Lys Pro Tyr
 Cys Met Tyr
 Pro Phe Leu Ser Gly Leu Leu Ser Ser

 1
 5
 5
 10
 10
 15
 15

 Leu Leu Phe Trp Leu Glu Ser Leu Met Leu Leu Cys Val Gln Met Val
 20
 25
 30
 30

 Leu Phe Leu Met Leu Met Leu Cys Val Leu Asp Tyr Arg Ile Tyr Cys Ile Lys
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 Ile Tyr Val Ser Ile Ile Leu Leu Met Ser Ile Trp Ile Ile Ser Ile
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<210> 260 <211> 65 <212> PRT <213> Homo sapiens

<210> 261 <211> 193 <212> PRT <213> Homo sapiens

<400> 261 Met Leu Met Tyr Arg Gly Glu Ala Leu Glu Asp Phe Thr Gly Pro Asp 10 Cys Arg Phe Val Asn Phe Lys Lys Gly Asp Pro Val Tyr Val Tyr 20 25 Lys Leu Ala Arg Gly Trp Pro Glu Val Trp Ala Gly Ser Val Gly Arg 35 40 Thr Phe Gly Tyr Phe Pro Lys Asp Leu Ile Gln Val Val His Glu Tyr 55 60 Thr Lys Glu Glu Leu Gln Val Pro Thr Asp Glu Thr Asp Phe Val Cys 70 75 Phe Asp Gly Gly Arg Asp Asp Phe His Asn Tyr Asn Val Glu Glu Leu 90 Leu Gly Phe Leu Glu Leu Tyr Asn Ser Ala Ala Thr Asp Ser Glu Lys 100 105 Ala Val Glu Gln Thr Leu Gln Asp Met Glu Lys Asn Pro Glu Leu Ser

Leu Lys Ala His Val Gln Ile Val Leu Tyr Trp Val Phe Leu Trp Ser
35 40 45

Arg Gly Asn Asn Phe Leu Thr
50 55

<210> 256 <211> 52 <212> PRT <213> Homo sapiens

<210> 257 <211> 55 <212> PRT <213> Homo sapiens

<210> 258 <211> 86 <212> PRT <213> Homo sapiens

<400> 258 Met Trp Pro Gly Cys Gln Val Leu Arg Ala Gly Leu Ser Pro Ala Gly 5 Arg Ala Arg Phe Pro Pro Asp Thr Tyr Leu Pro Ser Pro Arg Gln Gly 20 25 30 Gly Asn Pro Ala Cys Arg Cys Val Thr Ala Met Asn Ala Val Leu Gln 35 40 45 Val Leu Pro His Pro Ala Pro Asp Thr Asn Arg Ala Asp Glu Gly Cys 55 60 Gly Asp Gln Glu Gly Ser Arg Glu Leu Pro Pro Gly Gly Ala Ala Leu Gly His Arg Gly Gln 85

<213> Homo sapiens

<400> 252 Met Glu Thr Asp Pro Ala Ser Trp Pro Gln Pro Glu Pro Ala Gln Leu 10 Pro Gly Leu Tyr Ala Asp Phe Arg Ser Arg Thr Pro Arg Asp Ala Pro 20 25 30 Ala Gly Cys Pro Arg Trp Gly Trp Arg Cys Leu Ser Ala Ala Gln Pro 40 45 Ser Thr Gly Arg Thr Gly Glu Gly Ala Gly Pro Pro Gly Leu Cys Ala 55 Asp Gln Pro Cys Gly Ala Ala Ala Gly Gly Gly Ala Glu Lys Gln 70 Pro Ala Arg Ala Cys Gly Gly Asp Cys Trp Gly Gly Pro Met Pro His 85 Gly Arg Glu Pro Glu Ser Gly Ser Ala Ala Lys Val Ser Val Cys Pro Gly Glu Glu \* 115

<210> 253 <211> 27 <212> PRT

<213> Homo sapiens

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<210> 255 <211> 55 <212> PRT <213> Homo sapiens

 $<\!400\!>$  255 Met Tyr Met Asn Thr Cys Leu Tyr Leu His Val Tyr Val Leu Thr Cys 1 5 10 15 Ser Gly Cys Asn Val Asp Met Cys Ser Arg Leu Phe Leu Ser Thr Lys 20 25 30

Gly Glu Ser Val Thr Ala Met Glu Leu Glu Phe Lys Leu Leu Ala Ser 1635 1640 1645 Ser Lys Ala His Thr Ser Arg Phe Ile Ser Ala Asn Leu Pro Cys Asn 1650 1655 1660 Lys Phe Lys Asn Arg Leu Val Asn Ile Met Pro Tyr Glu Leu Thr Arg 1665 1670 1675 1680 Val Cys Leu Gln Pro Ile Arg Gly Val Glu Gly Ser Asp Tyr Ile Asn 1685 1690 1695 Ala Ser Phe Leu Asp Gly Tyr Arg Gln Gln Lys Ala Tyr Ile Ala Thr 1700 1705 1710 Gln Gly Pro Leu Ala Glu Ser Thr Glu Asp Phe Trp Arg Met Leu Trp 1715 1720 1725 Glu His Asn Ser Thr Ile Ile Val Met Leu Thr Lys Leu Arg Glu Met 1730 1735 1740 Gly Arg Glu Lys Cys His Gln Tyr Trp Pro Ala Glu Arg Ser Ala Arg 1745 1750 1755 1760 Tyr Gln Tyr Phe Val Val Asp Pro Met Ala Glu Tyr Asn Met Pro Gln 1765 1770 1775 Tyr Ile Leu Arg Glu Phe Lys Val Thr Asp Ala Arg Asp Gly Gln Ser 1780 1785 1790 Arg Thr Ile Arg Gln Phe Gln Phe Thr Asp Trp Pro Glu Gln Gly Val 1795 1800 1805 Pro Lys Thr Gly Glu Gly Phe Ile Asp Phe Ile Gly Gln Val His Lys 1810 1815 1820 Thr Lys Glu Gln Phe Gly Gln Asp Gly Pro Ile Thr Val His Cys Ser 1825 1830 1835 1840 Ala Gly Val Gly Arg Thr Gly Val Phe Ile Thr Leu Ser Ile Val Leu 1845 1850 1855 Glu Arg Met Arg Tyr Glu Gly Val Val Asp Met Phe Gln Thr Val Lys 1860 1865 1870 Thr Leu Arg Thr Gln Arg Pro Ala Met Val.Gln Thr Glu Asp Gln Tyr 1875 1880 1885 Gln Leu Cys Tyr Arg Ala Ala Leu Glu Tyr Leu Gly Ser Phe Asp His 1890 1895 1900 Tyr Ala Thr \* 1905 1907

<210> 251

<211> 94

<212> PRT

<213> Homo sapiens

<400> 251

Met Ile Trp Ile Tyr Phe Ala Phe Ile Phe Gln Arg Leu His Leu Ile 1 5 10 Pro Gly Lys Ser Ser Ala Arg Gln Val Ser Gly Phe Ser Leu Leu Ser 20 25 30 Phe Asn Pro Ser Asn Thr Ile Phe Val Lys Leu Asp Trp Trp Cys Phe 35 40 45 Ile Gln Leu Ile Tyr Ser Ala Tyr Leu Phe Glu Lys Arg Leu Leu Glu 50 55 60 Ile Asp Asp Val Phe Val Pro Val Ile Leu Lys Val Val Gly Ala Arg 70 . 75 Ile Glu Phe His Ser Gly Ile Gly Phe Gly Ser Gly Leu 85 90

<210> 252 <211> 116

<212> PRT

Pro His Val Gln Asp Pro Ser Leu Val Arg Trp Phe Tyr Ile Val Val 1125 1130 Val Pro Ile Asp Arg Val Gly Gly Ser Met Leu Thr Pro Arg Trp Ser 1140 1145 1150 Thr Pro Glu Glu Leu Glu Leu Asp Glu Leu Leu Glu Ala Ile Glu Gln 1155 1160 1165 Gly Glu Glu Gln Arg Arg Arg Arg Gln Ala Glu Arg Leu Lys 1175 1180 Pro Tyr Val Ala Ala Gln Leu Asp Val Leu Pro Glu Thr Phe Thr Leu 1190 1195 1200 Gly Asp Lys Lys Asn Tyr Arg Gly Phe Tyr Asn Arg Pro Leu Ser Pro 1205 1210 1215 Asp Leu Ser Tyr Gln Cys Phe Val Leu Ala Ser Leu Lys Glu Pro Met 1225 1220 1230 Asp Gln Lys Arg Tyr Ala Ser Ser Pro Tyr Ser Asp Glu Ile Val Val 1235 1240 1245 Gln Val Thr Pro Ala Gln Gln Glu Glu Pro Glu Met Leu Trp Val 1250 1255 1260 Thr Gly Pro Val Leu Ala Val Ile Leu Ile Leu Ile Val Ile Ala 1270 1275 1280 Ile Leu Leu Phe Lys Arg Lys Arg Thr His Ser Pro Ser Ser Lys Asp 1285 1290 1295 Glu Gln Ser Ile Gly Leu Lys Asp Ser Leu Leu Ala His Ser Ser Asp 1300 1305 Pro Val Glu Met Arg Arg Leu Asn Tyr Gln Thr Pro Gly Met Arg Asp 1315 1320 1325 His Pro Pro Ile Pro Ile Thr Asp Leu Ala Asp Asn Ile Glu Arg Leu 1335 1340 Lys Ala Asn Asp Gly Leu Lys Phe Ser Gln Glu Tyr Glu Ser Ile Asp 1350 1355 Pro Gly Gln Gln Phe Thr Trp Glu Asn Ser Asn Leu Glu Val Asn Lys 1365 1370 1375 Pro Lys Asn Arg Tyr Ala Asn Val Ile Ala Tyr Asp His Ser Arg Val 1380 1385 1390 Ile Leu Thr Ser Ile Asp Gly Val Pro Gly Ser Asp Tyr Ile Asn Ala 1395 1400 1405 Asn Tyr Ile Asp Gly Tyr Arg Lys Gln Asn Ala Tyr Ile Ala Thr Gln 1420 1415 Gly Pro Leu Pro Glu Thr Met Gly Asp Phe Trp Arg Met Val Trp Glu 1430 1435 1440 Gln Arg Thr Ala Thr Val Val Met Met Thr Arg Leu Glu Glu Lys Ser 1450 . 1455 1445 Arg Val Lys Cys Asp Gln Tyr Trp Pro Ala Arg Gly Thr Glu Thr Cys 1460 1465 1470 Gly Leu Ile Gln Val Thr Leu Leu Asp Thr Val Glu Leu Ala Thr Tyr 1475 1480 1485 Thr Val Arg Thr Phe Ala Leu His Lys Ser Gly Ser Ser Glu Lys Arg 1495 1500 Glu Leu Arg Gln Phe Gln Phe Met Ala Trp Pro Asp His Gly Val Pro 1510 1515 Glu Tyr Pro Thr Pro Ile Leu Ala Phe Leu Arg Arg Val Lys Ala Cys 1525 1530 Asn Pro Leu Asp Ala Gly Pro Met Val Val His Cys Ser Ala Gly Val 1545 1550 Gly Arg Thr Gly Cys Phe Ile Val Ile Asp Ala Met Leu Glu Arg Met 1560 1565 Lys His Glu Lys Thr Val Asp Ile Tyr Gly His Val Thr Cys Met Arg 1570 1575 1580 Ser Gln Arg Asn Tyr Met Val Gln Thr Glu Asp Gln Tyr Val Phe Ile 1585 1590 1595 His Glu Ala Leu Leu Glu Ala Ala Thr Cys Gly His Thr Glu Val Pro 1605 1610 1615 Ala Arg Asn Leu Tyr Ala His Ile Gln Lys Leu Gly Gln Val Pro Pro 1620 1625

Pro Pro Gln Lys Val Met Cys Val Ser Met Gly Ser Thr Thr Val Arg 615 Val Ser Trp Val Pro Pro Ala Asp Ser Arg Asn Gly Val Ile Thr 630 635 Gln Tyr Ser Val Ala Tyr Glu Ala Val Asp Gly Glu Asp Arg Gly Arg 645 650 His Val Val Asp Gly Ile Ser Arg Glu His Ser Ser Trp Asp Leu Val Gly Leu Glu Lys Trp Thr Glu Tyr Arg Val Trp Val Arg Ala His Thr 685 680 Asp Val Gly Pro Gly Pro Glu Ser Ser Pro Val Leu Val Arg Thr Asp 700 695 Glu Asp Val Pro Ser Gly Pro Pro Arg Lys Val Glu Val Glu Pro Leu . 715 710 Asn Ser Thr Ala Val His Val Tyr Trp Lys Leu Pro Val Pro Ser Lys 725 730 Gln His Gly Gln Ile Arg Gly Tyr Gln Val Thr Tyr Val Arg Leu Glu 745 Asn Gly Glu Pro Arg Gly Leu Pro Ile Ile Gln Asp Val Met Leu Ala 765 755 760 Glu Ala Gln Trp Arg Pro Glu Glu Ser Glu Asp Tyr Glu Thr Thr Ile 780 770 775 Ser Gly Leu Thr Pro Glu Thr Thr Tyr Ser Val Thr Val Ala Ala Tyr 790 795 Thr Thr Lys Gly Asp Gly Ala Arg Ser Lys Pro Lys Ile Val Thr Thr 805 810 Thr Gly Ala Val Pro Gly Arg Pro Thr Met Met Ile Ser Thr Thr Ala 820 825 830 Met Asn Thr Ala Leu Leu Gln Trp His Pro Pro Lys Glu Leu Pro Gly 835 840 845 Glu Leu Leu Gly Tyr Arg Leu Gln Tyr Cys Arg Ala Asp Glu Ala Arg 855 860 Pro Asn Thr Ile Asp Phe Gly Lys Asp Asp Gln His Phe Thr Val Thr 870 875 Gly Leu His Lys Gly Thr Thr Tyr Ile Phe Arg Leu Ala Ala Lys Asn 890 Arg Ala Gly Leu Gly Glu Glu Phe Glu Lys Glu Ile Arg Thr Pro Glu 905 Asp Leu Pro Ser Gly Phe Pro Gln Asn Leu His Val Thr Gly Leu Thr 915 920 925 Thr Ser Thr Thr Glu Leu Ala Trp Asp Pro Pro Val Leu Ala Glu Arg 935 940 Asn Gly Arg Ile Ile Ser Tyr Thr Val Val Phe Arg Asp Ile Asn Ser 950 955 Gln Gln Glu Leu Gln Asn Ile Thr Thr Asp Thr Arg Phe Thr Leu Thr 965 970 Gly Leu Lys Pro Asp Thr Thr Tyr Asp Ile Lys Val Arg Ala Trp Thr 985 Ser Lys Gly Ser Gly Pro Leu Ser Pro Ser Ile Gln Ser Arg Thr Met 995 1000 1005 Pro Val Glu Gln Val Phe Ala Lys Asn Phe Arg Val Ala Ala Ala Met 1010 1015 1020 Lys Thr Ser Val Leu Leu Ser Trp Glu Val Pro Asp Ser Tyr Lys Ser 1030 . 1035 Ala Val Pro Phe Lys Ile Leu Tyr Asn Gly Gln Ser Val Glu Val Asp 1045 1050 1055 Gly His Ser Met Arg Lys Leu Ile Ala Asp Leu Gln Pro Asn Thr Glu 1060 1065 1070 Tyr Ser Phe Val Leu Met Asn Arg Gly Ser Ser Ala Gly Gly Leu Gln 1080 1085 His Leu Val Ser Ile Arg Thr Ala Pro Asp Leu Leu Pro His Lys Pro 1095 1100 Leu Pro Ala Ser Ala Tyr Ile Glu Asp Gly Arg Phe Asp Leu Ser Met 1110 1115

Arg Val Gln Arg Asp Glu Ala Ile Tyr Glu Cys Thr Ala Thr Asn Ser Leu Gly Glu Ile Asn Thr Ser Ala Lys Leu Ser Val Leu Glu Glu Glu Gln Leu Pro Pro Gly Phe Pro Ser Ile Asp Met Gly Pro Gln Leu Lys Val Val Glu Lys Ala Arg Thr Ala Thr Met Leu Cys Ala Ala Gly Gly Asn Pro Asp Pro Glu Ile Ser Trp Phe Lys Asp Phe Leu Pro Val Asp Pro Ala Thr Ser Asn Gly Arg Ile Lys Gln Leu Arg Ser Gly Ala Leu Gln Ile Glu Ser Ser Glu Glu Ser Asp Gln Gly Lys Tyr Glu Cys Val Ala Thr Asn Ser Ala Gly Thr Arg Tyr Ser Ala Pro Ala Asn Leu Tyr Val Arg Val Arg Val Ala Pro Arg Phe Ser Ile Pro Pro Ser Ser Gln Glu Val Met Pro Gly Gly Ser Val Asn Leu Thr Cys Val Ala Val Gly Ala Pro Met Pro Tyr Val Lys Trp Met Met Gly Ala Glu Glu Leu Thr Lys Glu Asp Glu Met Pro Val Gly Arg Asn Val Leu Glu Leu Ser Asn Val Val Arg Ser Ala Asn Tyr Thr Cys Val Ala Ile Ser Ser Leu Gly Met Ile Glu Ala Thr Ala Gln Val Thr Val Lys Ala Leu Pro Lys Pro Pro Ile Asp Leu Val Val Thr Glu Thr Thr Ala Thr Ser Val Thr Leu Thr Trp Asp Ser Gly Asn Ser Glu Pro Val Thr Tyr Tyr Gly Ile Gln Tyr Arg Ala Ala Gly Thr Glu Gly Pro Phe Gln Glu Val Asp Gly Val Ala Thr Thr Arg Tyr Ser Ile Gly Gly Leu Ser Pro Phe Ser Glu Tyr Ala Phe Arg Val Leu Ala Val Asn Ser Ile Gly Arg Gly Pro Pro Ser Glu Ala Val Arg Ala Arg Thr Gly Glu Gln Ala Pro Ser Ser Pro Pro Arg Arg Val Gln Ala Arg Met Leu Ser Ala Ser Thr Met Leu Val Gln Trp Glu Pro Pro Glu Glu Pro Asn Gly Leu Val Arg Gly Tyr Arg Val Tyr Tyr Thr Pro Asp Ser Arg Arg Pro Pro Asn Ala Trp His Lys His Asn Thr Asp Ala Gly Leu Leu Thr Thr Val Gly Ser Leu Leu Pro Gly Ile Thr Tyr Ser Leu Arg Val Leu Ala Phe Thr Ala Val Gly Asp Gly Pro Pro Ser Pro Thr Ile Gln Val Lys Thr Gln Gln Gly Val Pro Ala Gln Pro Ala Asp Phe Gln Ala Glu Val Glu Ser Asp Thr Arg Ile Gln Leu Ser Trp Leu Leu Pro Pro Gln Glu Arg Ile Ile Met Tyr Glu Leu Val Tyr Trp Ala Ala Glu Asp Glu Asp Gln Gln His Lys Val Thr Phe Asp Pro Thr Ser Ser Tyr Thr Leu Glu Asp Leu Lys Pro Asp Thr Leu Tyr Arg Phe Gln Leu Ala Ala Arg Ser Asp Met Gly Val Gly Val Phe Thr Pro Thr Ile Glu Ala Arg Thr Ala Gln Ser Thr Pro Ser Ala . 605

Thr Phe Trp Phe Asn Met Ala Asp Ala Ala Phe Gln Ser Leu Val Cys 870 875 Phe Ser Ile Pro Tyr Leu Ala Tyr Tyr Asp Ser Asn Val Asp Leu Phe 885 890 Thr Trp Gly Thr Pro Ile Val Thr Ile Ala Leu Leu Thr Phe Leu Leu 905 His Leu Gly Ile Glu Thr Lys Thr Trp Thr Trp Leu Asn Trp Ile Thr 915 920 925 Cys Gly Phe Ser Val Leu Leu Phe Phe Thr Val Ala Leu Ile Tyr Asn 930 935 940 Ala Ser Cys Ala Thr Cys Tyr Pro Pro Ser Asn Pro Tyr Trp Thr Met 950 955 Gln Ala Leu Leu Gly Asp Pro Val Phe Tyr Leu Thr Cys Leu Met Thr 965 970 Pro Val Ala Ala Leu Leu Pro Arg Leu Phe Phe Arg Ser Leu Gln Gly 980 985 990 Arg Val Phe Pro Thr Gln Leu Gln Leu Ala Arg Gln Leu Thr Arg Lys 995 1000 1005 Ser Pro Arg Arg Cys Ser Ala Pro Lys Glu Thr Phe Ala Gln Gly Arg 1010 1015 1020 Leu Pro Lys Asp Ser Gly Thr Glu His Ser Ser Gly Arg Thr Val Lys 1030 1035 Thr Ser Val Pro Leu Ser Gln Pro Ser Trp His Thr Gln Gln Pro Val 1045 1050 1055 Cys Ser Leu Glu Ala Ser Gly Glu Pro Ser Thr Val Asp Met Ser Met 1060 1065 1070 Pro Val Arg Glu His Thr Leu Leu Glu Gly Leu Ser Ala Pro Ala Pro 1075 1080 1085 Met Ser Ser Ala Pro Gly Glu Ala Val Leu Arg Ser Pro Gly Gly Cys 1090 1095 1100 Pro Glu Glu Ser Lys Val Arg Ala Ala Ser Thr Gly Arg Val Thr Pro 1105 1110 1115 1120 Leu Ser Ser Leu Phe Ser Leu Pro Thr Phe Ser Leu Leu Asn Trp Ile 1125 1130 1135 Ser Ser Trp Ser Leu Val Ser Arg Leu Gly Ser Val Leu Gln Phe Ser 1140 1145 1150 Arg Thr Glu Gln Leu Ala Asp Gly Gln Ala Gly Arg Gly Leu Pro Val 1155 1160 1165 Gln Pro His Ser Gly Arg Ser Gly Leu Gln Gly Pro Asp His Arg Leu 1170 1175 1180 Leu Ile Gly Ala Ser Ser Arg Arg Ser Gln \* 1190 1194

<210> 250 <211> 1908 <212> PRT <213> Homo sapiens

<400> 250

Met Ala Pro Glu Pro Ala Pro Gly Arg Thr Met Val Pro Leu Val Pro 10 Ala Leu Val Met Leu Gly Leu Val Ala Gly Ala His Gly Asp Ser Lys 25 20 Pro Val Phe Ile Lys Val Pro Glu Asp Gln Thr Gly Leu Ser Gly Gly 35 40 Val Ala Ser Phe Val Cys Gln Ala Thr Gly Glu Pro Lys Pro Arg Ile 55 60 Thr Trp Met Lys Lys Gly Lys Lys Val Ser Ser Gln Arg Phe Glu Val 70 75 Ile Glu Phe Asp Asp Gly Ala Gly Ser Val Leu Arg Ile Gln Pro Leu 90

Leu Gly Gln Pro Thr Ser Ala Ile Ala Ser Asn Gly Tyr Ser Ser Gln Ala Asp Asn Trp Ala Ser Glu Leu Ala Gln Glu Gln Glu Ser Glu Arg Glu Leu Arg Tyr Glu Ala Glu Ser Pro Asp Glu Ala Ala Leu Val Tyr 3.90 Ala Ala Arg Ala Tyr Asn Cys Val Leu Val Glu Arg Leu His Asp Gln Val Ser Val Glu Leu Pro His Leu Gly Arg Leu Thr Phe Glu Leu Leu His Thr Leu Gly Phe Asp Ser Val Arg Lys Arg Met Ser Val Val Ile Arg His Pro Leu Thr Asp Glu Ile Asn Val Tyr Thr Lys Gly Ala Asp Ser Val Val Met Asp Leu Leu Gln Pro Cys Ser Ser Val Asp Ala Arg Gly Arg His Gln Lys Lys Ile Arg Ser Lys Thr Gln Asn Tyr Leu Asn Val Tyr Ala Ala Glu Gly Leu Arg Thr Leu Cys Ile Ala Lys Arg Val Leu Ser Lys Glu Glu Tyr Ala Cys Trp Leu Gln Ser His Leu Glu Ala Glu Ser Ser Leu Glu Asn Ser Glu Glu Leu Leu Phe Gln Ser Ala Ile Arg Leu Glu Thr Asn Leu His Leu Leu Gly Ala Thr Gly Ile Glu Asp Arg Leu Gln Asp Gly Val Pro Glu Thr Ile Ser Lys Leu Arg Gln Ala Gly Leu Gln Ile Trp Val Leu Thr Gly Asp Lys Gln Glu Thr Ala Val Asn Ile Ala Tyr Ala Cys Lys Leu Leu Asp His Asp Glu Glu Val Ile Thr Leu Asn Ala Thr Ser Gln Glu Ala Cys Ala Ala Leu Leu Asp Gln Cys Leu Cys Tyr Val Gln Ser Arg Gly Pro Gln Arg Ala Pro Glu Lys Thr Lys Gly Lys Val Ser Met Arg Phe Ser Ser Leu Cys Pro Pro Ser Thr Ser Thr Ala Ser Gly Arg Arg Pro Ser Leu Val Ile Asp Gly Arg Ser Leu Ala Tyr Ala Leu Glu Lys Asn Leu Glu Asp Lys Phe Leu Phe Leu Ala Lys Gln Cys Arg Ser Val Leu Cys Cys Arg Ser Thr Pro Leu Gln Lys Ser Met Val Val Lys Leu Val Arg Ser Lys Leu Lys Ala Met Thr Leu Ala Ile Gly Asp Gly Ala Asn Asp Val Ser Met Ile Gln Val Ala Asp Val Gly Val Gly Ile Ser Gly Gln Glu Gly Met Gln Ala Val Met Ala Ser Asp Phe Ala Val Pro Lys Phe Arg Tyr Leu Glu Arg Leu Leu Ile Leu His Gly His Trp Cys Tyr Ser Arg Leu Ala Asn Met Val Leu Tyr Phe Phe Tyr Lys Asn Thr Met Phe Val Gly Leu Leu Phe Trp Phe Gln Phe Phe Cys Gly Phe Ser Ala Ser Thr Met Ile Asp Gln Trp Tyr Leu Ile Phe Phe Asn Leu Leu Phe Ser Ser Leu Pro Pro Leu Val Thr Gly Val Leu Asp Arg Asp Val Pro Ala Asn Val Leu Leu Thr Asn 840 . Pro Gln Leu Tyr Lys Ser Gly Gln Asn Met Glu Glu Tyr Arg Pro Arg 

<210> 249 <211> 1195 <212> PRT <213> Homo sapiens

<400> 249

Met Asn Cys Asp Val Leu Trp Cys Val Leu Leu Val Cys Met Ser 10 Leu Phe Ser Ala Val Gly His Gly Leu Trp Ile Trp Arg Tyr Gln Glu 20 25 Lys Lys Ser Leu Phe Tyr Val Pro Lys Ser Asp Gly Ser Ser Leu Ser 35 Pro Val Thr Ala Ala Val Tyr Ser Phe Leu Thr Met Ile Ile Val Leu 55 60 Gln Val Leu Ile Pro Ile Ser Leu Tyr Val Ser Ile Glu Ile Val Lys 70 75 Ala Cys Gln Val Tyr Phe Ile Asn Gln Asp Met Gln Leu Tyr Asp Glu 85 90 Glu Thr Asp Ser Gln Leu Gln Cys Arg Ala Leu Asn Ile Thr Glu Asp 105 100 110 Leu Gly Gln Ile Gln Tyr Ile Phe Ser Asp Lys Thr Gly Thr Leu Thr 115 120 125 Glu Asn Lys Met Val Phe Arg Arg Cys Thr Val Ser Gly Val Glu Tyr 135 140 Ser His Asp Ala Asn Ala Gln Arg Leu Ala Arg Tyr Gln Glu Ala Asp 150 155 Ser Glu Glu Glu Val Val Pro Arg Gly Gly Ser Val Ser Gln Arg 165 170 175 Gly Ser Ile Gly Ser His Gln Ser Val Arg Val Val His Arg Thr Gln 180 185 190 Ser Thr Lys Ser His Arg Arg Thr Gly Ser Arg Ala Glu Ala Lys Arg 195 200 205 Ala Ser Met Leu Ser Lys His Thr Ala Phe Ser Ser Pro Met Glu Lys 215 220 Asp Ile Thr Pro Asp Pro Lys Leu Leu Glu Lys Val Ser Glu Cys Asp 235 Lys Ser Leu Ala Val Ala Arg His Gln Glu His Leu Leu Ala His Leu 245 250 Ser Pro Glu Leu Ser Asp Val Phe Asp Phe Phe Ile Ala Leu Thr Ile 260 265 270 Cys Asn Thr Val Val Val Thr Ser Pro Asp Gln Pro Arg Thr Lys Val 280 . Arg Val Arg Phe Glu Leu Lys Ser Pro Val Lys Thr Ile Glu Asp Phe 290 295 300 Leu Arg Arg Phe Thr Pro Ser Cys Leu Thr Ser Gly Cys Ser Ser Ile 310 315 Gly Ser Leu Ala Ala Asn Lys Ser Ser His Lys Leu Gly Ser Ser Phe 325 330 Pro Ser Thr Pro Ser Ser Asp Gly Met Leu Leu Arg Leu Glu Glu Arg 340 345

Gly Ser Thr Ala Leu Lys Ala Glu Thr Ser Glu Arg Leu Arg Thr Val Leu Leu Asp Val Thr Asp Pro Glu Asn Val Lys Arg Thr Ala Gln Trp Val Lys Asn Gln Val Gly Glu Lys Gly Leu Trp Gly Leu Ile Asn Asn Ala Gly Val Pro Gly Val Leu Ala Pro Thr Asp Trp Leu Thr Leu Glu Asp Tyr Arg Glu Pro Ile Glu Val Asn Leu Phe Gly Leu Ile Ser Val Thr Leu Asn Met Leu Pro Leu Val Lys Lys Ala Gln Gly Arg Val Ile Asn Val Ser Ser Val Gly Gly Arg Leu Ala Ile Val Gly Gly Tyr Thr Pro Ser Lys Tyr Ala Val Glu Gly Phe Asn Asp Ser Leu Arg Arg Asp Met Lys Ala Phe Gly Val His Val Ser Cys Ile Glu Pro Gly Leu Phe Lys Thr Asn Leu Ala Asp Pro Val Lys Val Ile Glu Lys Lys Leu Ala Ile Trp Glu Gln Leu Ser Pro Asp Ile Lys Gln Gln Tyr Gly Glu Gly Tyr Ile Glu Lys Ser Leu Asp Lys Leu Lys Gly Asn Lys Ser Tyr Val Asn Met Asp Leu Ser Pro Val Val Glu Cys Met Asp His Ala Leu Thr Ser Leu Phe Pro Lys Thr His Tyr Ala Ala Gly Lys Asp Ala Lys Ile Phe Trp Ile Pro Leu Ser His Met Pro Ala Ala Leu Gln Asp Phe Leu Leu Lys Gln Lys Ala Glu Leu Ala Asn Pro Lys Ala Val \* 

<210> 248 <211> 241 <212> PRT <213> Homo sapiens

<400> 248

Met Ser Val Pro Thr Met Ala Trp Met Met Leu Leu Leu Gly Leu Leu Ala Tyr Gly Ser Gly Val Asp Ser Glu Thr Val Val Thr Gln Glu Pro Ser Phe Ser Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Leu Asn Ser Gly Ser Val Ser Asp Ser Phe Tyr Pro Ser Trp His Gln Gln Thr Pro Gly Gln Pro Pro Arg Thr Leu Ile Tyr Asn Thr His Ile Arg Ala Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Ile Val Gly Asn Lys Ala Ala Leu Thr Ile Thr Gly Ala Gln Ala Asp Asp Glu Cys Val Tyr Tyr Cys Val Leu Tyr Met Gly Asn Asp Ile Ser Leu Phe Gly Gly Gly Thr Arg Leu Thr Val Leu Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu 145 150 Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp 

Glu Ala Leu Leu Asp Glu Asp Thr Leu Phe Cys Gln Gly Leu Glu Val 40 Phe Tyr Pro Glu Leu Gly Asn Ile Gly Cys Lys Val Val Pro Asp Cys 60 Asn Asn Tyr Arg Gln Lys Ile Thr Ser Trp Met Glu Pro Ile Val Lys 70 Phe Pro Gly Ala Val Asp Gly Ala Thr Tyr Ile Leu Val Met Val Asp 85 90 95 Pro Asp Ala Pro Ser Arg Ala Glu Pro Arg Gln Arg Phe Trp Arg His • 105 100 Trp Leu Val Thr Asp Ile Lys Gly Ala Asp Leu Lys Glu Gly Lys Ile 120 Gln Gly Gln Glu Leu Ser Ala Tyr Gln Ala Pro Ser Pro Pro Ala His 135 140 Ser Gly Phe His Arg Tyr Gln Phe Phe Val Tyr Leu Gln Glu Gly Lys 150 155 Val Ile Ser Leu Leu Pro Lys Glu Asn Lys Thr Arg Gly Ser Trp Lys 165 170 Met Asp Arg Phe Leu Asn Arg Phe His Leu Gly Glu Pro Glu Ala Ser 180 185 190 Thr Gln Phe Met Thr Gln Asn Tyr Gln Asp Ser Pro Thr Leu Gln Ala 200 205 Pro Arg Gly Arg Ala Ser Glu Pro Lys His Lys Thr Arg Gln Arg \* 215 220

<210> 246 <211> 84 <212> PRT

<213> Homo sapiens

Gly Pro Val \*

<210> 247 <211> 320 <212> PRT <213> Homo sapiens

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<210> 244
<211> 308
<212> PRT
<213> Homo sapiens
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<400> 244 Met Thr Lys Ala Gly Ser Lys Gly Gly Asn Leu Arg Asp Lys Leu Asp 10 Gly Asn Glu Leu Asp Leu Ser Leu Ser Asp Leu Asn Glu Val Pro Val 20 25 Lys Glu Leu Ala Ala Leu Pro Lys Ala Thr Ile Leu Asp Leu Ser Cys 35 40 Asn Lys Leu Thr Thr Leu Pro Ser Asp Phe Cys Gly Leu Thr His Leu 50 55 60 Val Lys Leu Asp Leu Ser Lys Asn Lys Leu Gln Gln Leu Pro Ala Asp 70 Phe Gly Arg Leu Val Asn Leu Gln His Leu Asp Leu Leu Asn Asn Lys Leu Val Thr Leu Pro Val Ser Phe Ala Gln Leu Lys Asn Leu Lys Trp 100 105 110 Leu Asp Leu Lys Asp Asn Pro Leu Asp Pro Val Leu Ala Lys Val Ala 115 120 125 Gly Asp Cys Leu Asp Glu Lys Gln Cys Lys Gln Cys Ala Asn Lys Val 135 140 Leu Gln His Met Lys Ala Val Gln Ala Asp Gln Glu Arg Gln 150 155 Arg Arg Leu Glu Val Glu Arg Glu Ala Glu Lys Lys Arg Glu Ala Lys 165 170 Gln Arg Ala Lys Glu Ala Gln Glu Arg Glu Leu Arg Lys Arg Glu Lys 180 185 190 Ala Glu Glu Lys Glu Arg Arg Lys Glu Tyr Asp Ala Leu Lys Ala Val Lys Arg Glu Gln Glu Lys Lys Pro Lys Lys Glu Ala Asn Gln Ala 210 215 220 Pro Lys Ser Lys Ser Gly Ser Arg Pro Arg Lys Pro Pro Pro Arg Lys 225 230 240 His Thr Arg Ser Trp Ala Val Leu Lys Leu Leu Leu Leu Leu Leu 250 Phe Gly Val Ala Gly Gly Leu Val Ala Cys Arg Val Thr Glu Leu Gln 260 265 270 Gln Gln Pro Leu Cys Thr Ser Val Asn Thr Ile Tyr Asp Asn Ala Val 275 280 · 285 Gln Gly Leu Arg Arg His Glu Ile Leu Gln Trp Val Leu Gln Thr Asp 290 295 Ser Gln Gln \* 305 307

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<210> 245
<211> 224
<212> PRT
<213> Homo sapiens
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Val Gly Leu Pro Gly Gln Arg Gly Glu Arg Gly Phe Pro Gly Leu Pro 970 965 Gly Pro Ser Gly Glu Pro Gly Lys Gln Gly Pro Ser Gly Ala Ser Gly 985 990 Glu Arg Gly Pro Pro Gly Pro Met Gly Pro Pro Gly Leu Ala Gly Pro 995 1000 1005 Pro Gly Glu Ser Gly Arg Glu Gly Ala Pro Gly Ala Glu Gly Ser Pro 1010 1015 1020 Gly Arg Asp Gly Ser Pro Gly Ala Lys Gly Asp Arg Gly Glu Thr Gly 1030 1035 Pro Ala Gly Pro Pro Gly Ala Pro Gly Ala Pro Gly Ala Pro Gly Pro 1045 1050 1055 Val Gly Pro Ala Gly Lys Ser Gly Asp Arg Gly Glu Thr Gly Pro Ala 1065 1070 1060 Gly Pro Ala Gly Pro Val Gly Pro Val Gly Ala Arg Gly Pro Ala Gly 1075 1080 1085 Pro Gln Gly Pro Arg Gly Asp Lys Gly Glu Thr Gly Glu Gln Gly Asp 1090 1095 1100 Arg Gly Ile Lys Gly His Arg Gly Phe Ser Gly Leu Gln Gly Pro Pro 1115 1110 Gly Pro Pro Gly Ser Pro Gly Glu Gln Gly Pro Ser Gly Ala Ser Gly 1125 1130 Pro Ala Gly Pro Arg Gly Pro Pro Gly Ser Ala Gly Ala Pro Gly Lys 1150 1140 1145 Asp Gly Leu Asn Gly Leu Pro Gly Pro Ile Gly Pro Pro Gly Pro Arg 1155 1160 1165 Gly Arg Thr Gly Asp Ala Gly Pro Val Gly Pro Pro Gly Pro Pro Gly 1175 1180 Pro Pro Gly Pro Pro Gly Pro Pro Ser Ala Gly Phe Asp Phe Ser Phe 1190 1195 1200 Leu Pro Gln Pro Pro Gln Glu Lys Ala His Asp Gly Gly Arg Tyr Tyr 1205 1210 Arg Ala Asp Asp Ala Asn Val Val Arg Asp Arg Asp Leu Glu Val Asp 1220 1225 1230 Thr Thr Leu Lys Ser Leu Ser Gln Gln Ile Glu Asn Ile Arg Ser Pro 1235 1240 1245 Glu Gly Ser Arg Lys Asn Pro Ala Arg Thr Cys Arg Asp Leu Lys Met 1250 1255 1260 Cys His Ser Asp Trp Lys Ser Gly Glu Tyr Trp Ile Asp Pro Asn Gln 1270 1275 1280 Gly Cys Asn Leu Asp Ala Ile Lys Val Phe Cys Asn Met Glu Thr Gly 1285 1290 1295 Glu Thr Cys Val Tyr Pro Thr Gln Pro Ser Val Ala Gln Lys Asn Trp 1300 1305 1310 Tyr Ile Ser Lys Asn Pro Lys Asp Lys Arg His Val Trp Phe Gly Glu 1315 1320 1325 Ser Met Thr Asp Gly Phe Gln Phe Glu Tyr Gly Gly Gln Gly Ser Asp 1330 1335' 1340 Pro Ala Asp Val Ala Ile Gln Leu Thr Phe Leu Arg Leu Met Ser Thr 1350 1355 1360 Glu Ala Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser Val Ala Tyr 1365 1370 Met Asp Gln Gln Thr Gly Asn Leu Lys Lys Ala Leu Leu Gln Gly 1380 1385 1390 Ser Asn Glu Ile Glu Ile Arg Ala Glu Gly Asn Ser Arg Phe Thr Tyr 1395 1400 1405 Ser Val Thr Val Asp Gly Cys Thr Ser His Thr Gly Ala Trp Gly Lys 1415 1420 Thr Val Ile Glu Tyr Lys Thr Thr Lys Thr Ser Arg Leu Pro Ile Ile 1430 1435 Asp Val Ala Pro Leu Asp Val Gly Ala Pro Asp Gln Glu Phe Gly Phe 1445 1450 Asp Val Gly Pro Val Cys Phe Leu 1460 1464

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Gln Val Gly Tyr Gly Met Ala Ala Gly Tyr Thr Ile Phe Ile Thr Ser 215 220 Phe Leu Gly Val Leu Val Phe Ser Arg Cys Phe Arg Asp Thr Thr Met 230 235 Ile Met Ile Gly Met Val Ser Phe Gly Ser Gly Ala Leu Leu Leu Ala 245 250 Phe Val Lys Glu Thr Tyr Met Phe Tyr Ile Ala Arg Ala Val Met Leu 265 Phe Ala Leu Ile Pro Val Thr Thr Ile Arg Ser Ala Met Ser Lys Leu 275 280 285 Ile Lys Gly Ser Ser Tyr Gly Lys Val Phe Val Ile Leu Gln Leu Ser 290 295 300 Leu Ala Leu Thr Gly Val Val Thr Ser Thr Leu Tyr Asn Lys Ile Tyr 310 315 Gln Leu Thr Met Asp Met Phe Val Gly Ser Cys Phe Ala Leu Ser Ser 325 330 335 Phe Leu Ser Phe Leu Ala Ile Ile Pro Ile Ser Ile Val Ala Tyr Lys 340 345 Gln Val Pro Leu Ser Pro Tyr Gly Asp Ile Ile Glu Lys \* 360

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Arg Tyr Arg Ile Leu Leu Val Thr Val Leu Trp Thr Leu Leu Val Tyr 340 Ser Met Leu Ser His Lys Glu Phe Arg Phe Ile Tyr Pro Val Leu Pro 360 Phe Cys Met Val Phe Cys Gly Tyr Ser Leu Thr His Leu Lys Thr Trp 375 380 Lys Lys Pro Ala Leu Ser Phe Leu Phe Leu Ser Asn Leu Phe Leu Ala 390 395 Leu Tyr Thr Gly Leu Val His Gln Arg Gly Thr Leu Asp Val Met Ser 405 410 His Ile Gln Lys Val Cys Tyr Asn Asn Pro Asn Lys Ser Ser Ala Ser 420 425 430 Ile Phe Ile Met Met Pro Cys His Ser Thr Pro Tyr Tyr Ser His Val 435 440 His Cys Pro Leu Pro Met Arg Phe Leu Gln Cys Pro Pro Asp Leu Thr 455 460 Gly Lys Ser His Tyr Leu Asp Glu Ala Asp Val Phe Tyr Leu Asn Pro 465 470 475 Leu Asn Trp Leu His Arg Glu Phe His Asp Asp Ala Ser Leu Pro Thr 485 490 His Leu Ile Thr Phe Ser Ile Leu Glu Glu Glu Ile Ser Ala Phe Leu 500 505 Ile Ser Ser Asn Tyr Lys Arg Thr Ala Val Phe Phe His Thr His Leu 515 520 Pro Glu Gly Arg Ile Gly Ser His Ile Tyr Val Tyr Glu Arg Lys Leu 535 Lys Gly Lys Phe Asn Met Lys Met Lys Phe 545 550

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Leu Arg Asp Ala Asp Asp Leu Gln Lys Arg Leu Ala Val Tyr Gln Ala 200 Gly Ala Arg Glu Gly Ala Glu Arg Gly Leu Ser Ala Ile Arg Glu Arg 215 220 Leu Gly Pro Leu Val Glu Gln Gly Pro Arg Ala Gly Arg His Cys Gly 230 235 Leu Pro Gly Pro Ala Ser Arg Tyr Arg Ser Gly Pro Arg Pro Gly Ala 245 250 Ser Gly Cys Ala Arg Gly Trp Arg Arg Trp Ala Ala Gly Pro Ala Thr 260 265 Ala Trp Thr Arg 275 276

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<213> Homo sapiens

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Ala Lys Val Leu Glu Arg Gly Lys Asp Ala Thr Leu Gln Lys Gln Glu Asp Val Ala Val Ala Ala Val Leu Glu Ser Leu Leu Lys Leu Ala Leu Leu Ala Gly Leu Thr Ile Thr Val Phe Gly Phe Ala Tyr Ser Gln Leu Ala Leu Asp Ile Tyr Gly Gly Thr Met Leu Ser Ser Gly Ser Gly Pro Val Leu Leu Arg Ser Tyr Cys Leu Tyr Val Leu Leu Leu Ala Ile Asn Gly Val Thr Glu Cys Phe Thr Phe Ala Ala Met Ser Lys Glu Glu Val Asp Arg Tyr Asn Phe Val Met Leu Ala Leu Ser Ser Ser Phe Leu Val Leu Ser Tyr Leu Leu Thr Arg Trp Cys Gly Ser Val Gly Phe Ile Leu Ala Asn Cys Phe Asn Met Gly Ile Arg Ile Thr Gln Ser Leu Cys Phe Ile His Arg Tyr Tyr Arg Arg Ser Pro His Arg Pro Leu Ala Gly Leu His Leu Ser Pro Val Leu Leu Gly Thr Phe Ala Leu Ser Gly Gly Val Thr Ala Val Ser Glu Val Phe Leu Cys Cys Glu Gln Gly Trp Pro Ala Arg Leu Ala His Ile Ala Val Gly Ala Phe Cys Leu Gly Ala Thr Leu Gly Thr Ala Phe Leu Thr Glu Thr Lys Leu Ile His Phe Leu Arg Thr Gln Leu Gly Val Pro Arg Arg Thr Asp Lys Met Thr  $\,\,$   $\,$ 

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Lys Tyr Leu Val Lys His Cys Gly Asn Ile Pro Val Phe Val Ile Asn 360 Tyr Pro Leu Thr Leu Lys Pro Phe Tyr Met Arg Asp Asn Glu Asp Gly 375 380 Pro Gln His Thr Val Ala Ala Val Asp Leu Leu Val Pro Gly Val Gly 390 395 Glu Leu Phe Gly Gly Gly Leu Arg Glu Glu Arg Tyr His Phe Leu Glu 405 410 Glu Arg Leu Ala Arg Tyr Leu Asp Leu Arg Arg Phe Gly Ser Val Pro 425 420 His Gly Gly Phe Gly Met Gly Phe Glu Arg Tyr Leu Gln Cys Ile Leu 435 440 445 Gly Val Asp Asn Ile Lys Asp Val Ile Pro Phe Pro Arg Phe Pro His Ser Cys Leu Leu \* 468

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345

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115

Tyr Glu Trp Leu Phe Glu Met Leu Leu \* 110

569

WO 01/55437 PCT/US01/0	2623
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tca gaa aag cag caa ata atg gaa aag cat tat ggc ttc aat gaa ata Ser Glu Lys Gln Gln Ile Met Glu Lys His Tyr Gly Phe Asn Glu Ile 555 560 570	1791
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agt cat gca Ser His Ala	ttg aga Leu Arg 335	Lys Gln	gca t Ala :	tgg aa Trp Ly 34	s Phe	ctt Leu	ctg Leu	ggt Gly	tat Tyr 345	ttt Phe	1119
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gaa aaa gat Glu Lys Asp 395											1311
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att ata tat gaa caa gaa gga gta tat att cac tca tct tgt gga aag	159

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	s Glu Gly G			cct ttt aca go Pro Phe Thr A	
tgc acc at Cys Thr Il- 75		aa cttttg ( *	ctatttaata c	aaatacttt gggca	atgeet 418
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Phe Ser Pro Gly \*
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413

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	Lys Ala Gly A		tca tct caa gat gac Ser Ser Gln Asp Asp 25	216
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Glu Ser Val Arg Leu Asn Glu Thr Leu Ser Ser Phe Ser Asp Asn Asn
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Lys Ile Thr Ile Arg Leu Gly Arg Ala Leu Lys Lys Gly Glu Tyr Arg
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                                      90
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Val Lys Val Tyr Gln Leu Leu Val Asn Glu Gln Glu Pro Cys Lys Phe
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Leu Leu Asp Ala Val Phe Ala Lys Gly Met Thr Val Arg Gln Ser Lys
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ctg Leu	ccc Pro	ttg Leu	gag Glu	cca Pro 635	gjà aaa	ggc	tgc Cys	ata Ile	gac Asp 640	ttt Phe	cag Gln	aca Thr	gag Glu	aac Asn 645	agc Ser	2095
tcc Ser	cgg Arg	cac His	tgt Cys 650	Leu	gtg Val	acc Thr	tac Tyr	agg Arg 655	cct Pro	gat Asp	aaa Lys	aat Asn	cac His 660	Thr	acc Thr	2143
ata Ile	cga Arg	agt Ser 665	Val	ctg Leu	atg Met	gaa Glu	atg Met 670	Ser	tac Tyr	cga Arg	ctg Leu	gat Asp 675	Asp	act Thr	gga Gly	2191
aat Asn	cca Pro 680	Ile	tgc Cys	tcc Ser	tgc Cys	cag Gln 685	Pro	gta Val	cat His	aca Thr	ttt Phe 690	Phe	gga Gly	gga Gly	cct Pro	2239
act Thr 695	Cys	aaa Lys	cta Leu	ttg Leu	acc Thr 700	Lys	aat Asn	gcc Ala	att	Phe	Gln	ago Ser	cca Pro	gag Glu	aat Asn 710	2287
					Val					Glu					gcc Ala	2335
ctg Leu	ctg Leu	tgg Trp	gat Asp 730	Ala	gcc Ala	agt Ser	ggc	tcg Ser 735	Leu	ctc Leu	cag Gl	gac Asp	cta Leu 740	Gln	acc Thr	2383

gca Ala	gag Glu	gaa Glu	tct Ser	gga Gly 235	gct Ala	gtc Val	att Ile	tta Leu	gaa Glu 240	gag Glu	caa Gln	cta Leu	gca Ala	ggt Gly 245	gtc Val	895
tca Ser	gca Ala	gag Glu	caa Gln 250	gaa Glu	gtt Val	aca Thr	tgt Cys	atc Ile 255	gat Asp	gga Gly	ggc Gly	aag Lys	acc Thr 260	ctc Leu	ccc Pro	943
aaa Lys	cag Gln	cca Pro 265	tct Ser	ccc Pro	cag Gln	aag Lys	tct Ser 270	gag Glu	cct Pro	ctg Leu	cta Leu	cct Pro 275	tct Ser	gct Ala	tct Ser	991
atg Met	gat Asp 280	gag Glu	gaa Glu	gaa Glu	GJA 333	gac Asp 285	act Thr	tgt Cys	aca Thr	ata Ile	tgt Cys 290	ctg Leu	gaa Glu	cag Gln	tgg Trp	1039
acc Thr 295	aat Asn	gct Ala	GJÀ aaa	gac Asp	cac His 300	cgg Arg	ctc Leu	tca Ser	gca Ala	tta Leu 305	cgc Arg	tgt Cys	gly ggg	cat His	ctc Leu 310	1087
Phe	Gly	Tyr	Arg	Cys 315	att Ile	Ser	Thr	Trp	Leu 320	Lys	Gly	Gln	Val	Arg 325	Lys	1135
tgt Cys	ccc Pro	cag Gln	tgc Cys 330	aac Asn	aag Lys	aaa Lys	gcc Ala	agg Arg 335	cac His	agt Ser	gac Asp	att Ile	gtc Val 340	gtc Val	ctt Leu	1183
Tyr	Ala	Arg 345	Thr	Leu	aga Arg	Ala	Leu 350	Asp	Thr	Ser	Glu	Gln 355	Glu	Arg	Met	1231
Lys	Ser 360	Ser	Leu	Leu	aag Lys	Glu 365	Gln	Met	Leu	Arg	Lys 370	Gln	Ala	Glu	Leu	1279
Glu 375	Ser	Ala	Gln	Cys	cga Arg 380	Leu	Gln	Leu	Gln	Val 385	Leu	Thr	Asp	Lys	Cys 390	1327
Thr	Arg	Leu	Gln	Arg 395		Val	Gln	Āsp	Leu 400	Gln	Lys	Leu	Thr	Ser 405	His	1375
Gln	Ser	Gln	Asn 410	Leu	Gln	Gln	Pro	Arg 415	Gly	Ser	Gln	Ala	Trp 420	Val	Leu	1423
Ser	Cys	Ser 425	Pro	Ser	Ser	Gln	Gly 430	Gln	His	Lys	His	Lys 435	Tyr	His	Phe	1471
Gln	Lys 440	Thr	Phe	Thr	Val	Ser 445	Gln	Ala	Gly	Asn	Cys 450	Arg	Ile	Met	gca Ala	1519
Tyr 455	Cys	Asp	Ala	Leu	Ser 460	Cys	Leu	Val	Ile	Ser 465	Gln	Pro	Ser	Pro	Gln 470	1567
					Gly					Met					aac Asn	1615

<400> 223 tgccgtaccg gtccggaatt cccgggtcga cgatttcgtg gcagttggcg taggtgcatt	60
cggagtgcgg ctgaggtaac taccgagtct tcggcggagg taactaccga gtcttcggcg	120
ggctcgcgag cccggccgcg gcctgctggt ttcagtg atg gct cat gaa gca atg Met Ala His Glu Ala Met 1 5	175
gaa tat gat gtt cag gtg cag tta aat cat gcc gaa caa cag cca gct Glu Tyr Asp Val Gln Val Gln Leu Asn His Ala Glu Gln Gln Pro Ala 10 15 20	223
cct gct ggc atg gcc agc agc caa ggg gga cca gcc ctc ctc cag cct Pro Ala Gly Met Ala Ser Ser Gln Gly Gly Pro Ala Leu Leu Gln Pro 25 30 35	271
gtt cct gct gat gtg gtc agc agc cag ggg gta cca tcc atc ctc cag Val Pro Ala Asp Val Val Ser Ser Gln Gly Val Pro Ser Ile Leu Gln 40 45 50	319
cca gct cct gct gag gtg atc agc agc caa gcg aca cca ccc ctg ctc Pro Ala Pro Ala Glu Val Ile Ser Ser Gln Ala Thr Pro Pro Leu Leu 55 60 65 70	367
cag cct gct ccg caa ctg tct gtt gac ctg aca gaa gtg gag gtc ttg Gln Pro Ala Pro Gln Leu Ser Val Asp Leu Thr Glu Val Glu Val Leu 75 80 85	415
gga gaa gac aat gtg gag aac atc aat cca aga act tca gaa caa cat Gly Glu Asp Asn Val Glu Asn Ile Asn Pro Arg Thr Ser Glu Gln His 90 95 100	463
agg cag gga tot gat ggt aat cac acc atc cca gca tot tog ttg cat Arg Gln Gly Ser Asp Gly Asn His Thr Ile Pro Ala Ser Ser Leu His 105 110 115	511
tca atg acc aac ttc atc agc gga ctg cag aga ctt cat ggc atg ctg Ser Met Thr Asn Phe Ile Ser Gly Leu Gln Arg Leu His Gly Met Leu 120 125 130	559
gaa ttc ctg aga cct tca tct tca aac cac agt gta ggg cca atg aga Glu Phe Leu Arg Pro Ser Ser Asn His Ser Val Gly Pro Met Arg 135 140 145 150	607
aca aga agg agg gta tot got toa ogg agg goa aga goo gga ggg tot Thr Arg Arg Arg Val Ser Ala Ser Arg Arg Ala Arg Ala Gly Gly Ser 155 160 165	655
cag agg aca gac agt gcc agg ttg aga gca cca ttg gat gct tac ttt Gln Arg Thr Asp Ser Ala Arg Leu Arg Ala Pro Leu Asp Ala Tyr Phe 170 175 180	703
cag gtg agc agg acc cag cct gac ttg cca gct acc act tat gat tca Gln Val Ser Arg Thr Gln Pro Asp Leu Pro Ala Thr Thr Tyr Asp Ser 185 190 195	751
gag act agg aat cct gta tct gaa gag ttg cag gtg tct agt agt tct Glu Thr Arg Asn Pro Val Ser Glu Glu Leu Gln Val Ser Ser Ser 200 205 210	799
gat tot gac agt gac age tot gca gag tat gga ggg gtt gtt gac cag Asp Ser Asp Ser Asp Ser Ser Ala Glu Tyr Gly Gly Val Val Asp Gln 215 220 225 230	847

wo	01/5	5437												P	CT/US	01/02623
Phe	Tyr	Tyr	Thr	Glu 325	Val	Gln	Leu	Lys	Glu 330	Glu	Ser	Ala	Ala	Ala 335	Ala	
gct Ala	gct Ala	gct Ala	gcc Ala 340	gca Ala	ggc Gly	acc Thr	cca Pro	gtc Val 345	cct Pro	GJA aaa	act Thr	ccc Pro	acc Thr 350	tcc Ser	gag Glu	1174
cca Pro	gct Ala	ccc Pro 355	acc Thr	ccc Pro	agc Ser	atg Met	act Thr 360	ggc Gly	ctg Leu	cct Pro	ctg Leu	tct Ser 365	gct Ala	ctt Leu	cca Pro	1222
cca Pro	cct Pro 370	ctg Leu	cac His	aaa Lys	gcc Ala	cag Gln 375	tcc Ser	tcc Ser	ggc Gly	cca Pro	gaa Glu 380	cat His	cct Pro	ggc Gly	ccg Pro	1270
						gly aaa										1318
						gat Asp										1366
_			_			cac His				-	-	_		-	-	1414
_			-	_	_	tct Ser			-	_		-		_		1462
_		-			_	cag Gln 455		_			_				_	1510
	-					cgg Arg	_	_	_		_			_	-	1558
_				-	_	cgc Arg	_								-	1606
_		_	_		_	cgg Arg		_	_	_	_	_	_		_	1654
gac Asp	_	gct	gtgc	tgc i	aggt	tcta	ct c	tgtt	cctg	g cc	ctgc	cggc	agc	cact	gac	1710

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<212> DNA

<213> Homo sapiens

<220>

<221> CDS <222> (158)..(2479)

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cac His	agc Ser	tgg Trp	atg Met 100	gag Glu	ggt Gly	cag Gln	gtg Val	acc Thr 105	gtc Val	tgg Trp	ctg Leu	ctg Leu	gag Glu 110	cag Gln	aag Lys	454
ctg Leu	cag Gln	gtc Val 115	tgc Cys	tgc Cys	agg Arg	gtg Val	gag Glu 120	gag Glu	gtg Val	tgg Trp	ctg Leu	gca Ala 125	gag Glu	ctg Leu	cag Gln	502
ggc	ccc Pro 130	tgt Cys	ccc Pro	cag Gln	gca Ala	cca Pro 135	ccc Pro	ctg Leu	gag Glu	ccc Pro	gga Gly 140	gcc Ala	cag Gln	gcc Ala	ctg Leu	. 550
gcc Ala 145	tac Tyr	agg Arg	ccc Pro	gtc Val	tcc Ser 150	agg Arg	aac Asn	atc Ile	gat Asp	gtc Val 155	cca Pro	aag Lys	agg Arg	aag Lys	tcg Ser 160	598
gac Asp	gca Ala	gtg Val	gaa Glu	atg Met 165	gat Asp	gag Glu	atg Met	atg Met	gcg Ala 170	gcc Ala	atg Met	gtg Val	ctg Leu	acg Thr 175	tcc Ser	646
ctg Leu	tcc Ser	tgc Cys	agc Ser 180	cct Pro	gtt Val	gta Val	cag Gln	agt Ser 185	cct Pro	ccc Pro	Gly 333	acc Thr	gag Glu 190	gcc Ala	aac Asn	694
ttc Phe	tct Ser	gct Ala 195	tcc Ser	cgt Arg	gcg Ala	gcc Ala	tgc Cys 200	Asp	cca Pro	tgg Trp	aag Lys	gag Glu 205	agt Ser	ggt Gly	gac Asp	742
atc Ile	tcg Ser 210	Asp	agc Ser	Gly	agc Ser	agc Ser 215	act Thr	acc Thr	agc Ser	ggt Gly	cac His 220	tgg Trp	agt Ser	glà aaa	agc Ser	790
agt Ser 225	Gly	gtc Val	tcc Ser	acc Thr	CCC Pro 230	tcg Ser	ccc Pro	ccc Pro	cac His	ccc Pro 235	Gln	gcc Ala	agc Ser	ccc Pro	aag Lys 240	838
tat Tyr	ttg Leu	gly	gat Asp	gct Ala 245	Phe	ggt Gly	tct Ser	ccc Pro	caa Gln 250	Thr	gat Asp	cat His	ggc Gly	ttt Phe 255	gag Glu	886
acc Thr	gat Asp	cct Pro	gac Asp 260	Pro	ttc Phe	ctg Leu	ctg Leu	gac Asp 265	Glu	cca Pro	gct Ala	cca Pro	cga Arg 270	Lys	aga Arg	934
aag Lys	aac Asn	Ser 275	Val	aag Lys	gtg Val	atg Met	Tyr 280	Lys	tgc Cys	ctg Leu	tgg Trp	CCa Pro 285	Asn	tgt Cys	ggc	982
aaa Lys	gtt Val 290	Leu	cgc Arg	tcc Ser	att Ile	gtg Val 295	Gly	atc Ile	aaa Lys	cga Arg	cac His	Val	aaa Lys	gcc	ctc Leu	1030
cat His 305	Leu	ggg Gly	gac Asp	aca Thr	gtg Val 310	Asp	tct Ser	gat Asp	cag Gln	Phe 315	Lys	cgg Arg	gag	gag Glu	gat Asp 320	1078
ttc	tac	tac	aca	gag	gtg	cag	ctg	aag	gag	gaa	tct	gct	gct	gct	gct	1126

wo	01/5	5437							I	CT/US01/02	2623
			245			250			255	·	
						gaa Glu					816
						gag Glu					864

gag gaa gtg act ctg ccc aag ctg cga ggg ggc ctg atg acc atc gac 912
Glu Glu Val Thr Leu Pro Lys Leu Arg Gly Gly Leu Met Thr Ile Asp
290 295 300

ccc agc ctg gac aag cag aca gtg aac acc tac atg agc cag gcc ttc 960 Pro Ser Leu Asp Lys Gln Thr Val Asn Thr Tyr Met Ser Gln Ala Phe 305 310 315 320

cag ctc cct gag tcg gaa atg cca gag gag ggt gac gag aag gaa gaa 1008 Gln Leu Pro Glu Ser Glu Met Pro Glu Glu Gly Asp Glu Lys Glu Glu 325 330 335

gcc gtg gtg gaa atc ctc cag act gcc ctg gag cgg ctt cag gtg att 1056
Ala Val Val Glu Ile Leu Gln Thr Ala Leu Glu Arg Leu Gln Val Ile
340 345 350

gac atc agg cgt gtg gga cct cga gag cca gag cct gca agc tag 1101
Asp Ile Arg Arg Val Gly Pro Arg Glu Pro Glu Pro Ala Ser \*
355 360 365

<210> 222 <211> 1710 <212> DNA <213> Homo sapiens

<220> <221> CDS

<222> (119)..(1660)

<400> 222

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Ala Arg Val Leu Gly Pro Ser Ala Ser Glu Gly Pro Ser Ala Ala Pro
20 25 30

ccc tcg gag cca ctg cta gaa ggg gcc gct ccc cag cct ttc acc acc 262
Pro Ser Glu Pro Leu Leu Glu Gly Ala Ala Pro Gln Pro Phe Thr Thr
35 40 45

tct gat gac acc ccc tgc cag gag cag ccc aag gaa gtc ctt aag gct
Ser Asp Asp Thr Pro Cys Gln Glu Gln Pro Lys Glu Val Leu Lys Ala
50
60

ccc agc acc teg ggc ctt cag cag gtg gcc ttt cag cct ggg cag aag 358

Me	g cag		g cad	s Met						ı Arg					c tct e Ser	48
	_	_			_	_			_	_				tgg Trp		96
aag Lys	tgc Cys	aaa Lys 35	gat Asp	gtg Val	gtg Val	gct Ala	ggg Gly 40	ggc Gly	cca Pro	gag Glu	cgc Arg	tgg Trp 45	cag Gln	atg Met	ctg Leu	144
														gaa Glu		192
														ctg Leu		240
														gtg Val 95		288
	_	_		-	-	_	_		_				_	gat Asp	-	336
														gat Asp		384
														atg Met		432
														aac Asn		480
	_	_	_			_	-	_	_		_		-	gag Glu 175		528
														gag Glu		576
														cag Gln		624
														caa Gln		672
														aat Asn		720
														ggc Gly		768

WO 01/55437			PC	T/US01/02623
Lys Val Ile Ser 395	Val Ile Gly Gly 400	Leu Ala Ala	Cys Phe Ile Phe Va 405	al
ttc cca ggg ctg Phe Pro Gly Leu 410	tgc ctc att caa Cys Leu Ile Gln 415	gcc aaa ctc Ala Lys Leu	tot gag atg gaa ga Ser Glu Met Glu G 420	ag 1659 lu
gtc aaa cca gcc Val Lys Pro Ala 425	agc tgg tgg gtg Ser Trp Trp Val 430	ctg gtc agc Leu Val Ser 435	tac gga gtc ctc to Tyr Gly Val Leu Le 4	tg 1707 eu 40
gtc acc ctg gga Val Thr Leu Gly	gcc ttc atc ttc Ala Phe Ile Phe 445	ggc cag acc Gly Gln Thr 450	aca gcc aac gcc a Thr Ala Asn Ala I 455	tc 1755 le
ttt gtg gat ctc Phe Val Asp Leu 460	Leu Ala *	etgeeteee ag	ggaacaca aggeettt	gc 1808
cattggtcgc agga	acccat ctcttagago	tatggggcca	ttcttagtcc acgatc	attc 1868
caactggtgg gatg	acatec ggacatecto	ttccagggac	tggggcaaac tcaggc	ccca 1928
cacctctgga cago	tcaaat ccagtcccct	tectgetece	cagtcctggc agtgcc	gtgg 1988
atggcggcag gaag	rtctcac atcatagagg	g acceditecte	ctctcccagt tctcaa	cttc 2048
tccatgcctg gaat	ccacgg gtgaagagag	g teggtagate	tcataagaaa gaatcc	agtc 2108
tgacttccct ctgc	agaatg actatggac	a gaaggccacc	atcctccaca gagcac	cctg 2168
teetgagtag gggt	tgtgct cattacccc	a ggccagtggt	agetteetea ggagee	tggc 2228
cacttccaaa ggta	igcactg aagtcatgo	a aatacatagt	caggtagatt cagacc	ttgt 2288
ccacaccttc ctgg	ggcaac ccccaccat	g aacctgtcag	cctctttccc atagct	aata 2348
gacatttccc aggo	ettgag gggccccac	c ctgtctcttt	catcaaacct gatggt	ccag 2408
gctgggcatc cct	steetee tecatecee	a gacatcacca	ggtctaatgt ttacaa	acgg 2468
tgccagcccg gct	tgaage caagggeeg	t cccgtgccac	ggtgctgtga gtatto	ectcc 2528
gttagctttc ccca	ataaggt tgggagtat	c tgcttttgtg	tetgagatgg geecet	cttt 2588
tcagaggccg cag	ggtgggt gatggagaa	g gctgagaacc	tttcagaccc tctgtg	tggg 2648
ctgggctggt caga	atcagg gtgtacctc	c ccgacacctt	ctttttcagt gatgtt	ttct 2708
cttctccctg cct	tcctct gcctcctcc	c ctgccagccc	tagcgtgact acccag	gagac 2768
aaaaaaaaaa aaa	ıaa			2784

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cag Gln	cag Gln	gac Asp 155	aag Lys	att Ile	ata Ile	gct Ala	gtg Val 160	atg Met	gcg Ala	aaa Lys	gag Glu	ccg Pro 165	gag Glu	ggg Gly	gcc Ala	891
agc Ser	ggc Gly 170	cct Pro	tgg Trp	tac Tyr	aca Thr	gac Asp 175	cgc Arg	aag Lys	ttc Phe	acc Thr	atc Ile 180	agc Ser	ctc Leu	act Thr	gcc Ala	939
ttc Phe 185	ctc Leu	ttc Phe	atc Ile	ctg Leu	ccc Pro 190	ctc Leu	tcc Ser	atc Ile	ccc Pro	agg Arg 195	gag Glu	att Ile	ggt Gly	ttc Phe	cag Gln 200	987
aaa Lys	tat Tyr	gcc Ala	agc Ser	ttc Phe 205	ctg Leu	agc Ser	gtc Val	gtg Val	ggt Gly 210	acc Thr	tgg Trp	tac Tyr	gtc Val	aca Thr 215	gcc Ala	1035
atc Ile	gtt Val	atc Ile	atc Ile 220	aag Lys	tac Tyr	atc Ile	tgg Trp	cca Pro 225	gat Asp	aaa Lys	gag Glu	atg Met	acc Thr 230	cca Pro	ggg ggg	1083
aac Asn	atc Ile	ctg Leu 235	acc Thr	agg Arg	ccg Pro	gct Ala	tcc Ser 240	tgg Trp	atg Met	gct Ala	gtg Val	ttc Phe 245	aat Asn	gcc Ala	atg Met	1131
ccc Pro	acc Thr 250	atc Ile	tgc Cys	ttc Phe	gga Gly	ttt Phe 255	cag Gln	tgc Cys	cac His	gtc Val	agc Ser 260	agt Ser	gtg Val	ccc Pro	gtc Val	1179
									aag Lys							1227
									gtc Val 290							1275
				Thr					gtg Val							1323
tcc Ser	tat Tyr	ccc Pro 315	tcg Ser	gag Glu	gac <b>Asp</b>	atg Met	gcc Ala 320	gtg Val	gcc Ala	gtt Val	gcc Ala	cga Arg 325	gcc Ala	ttc Phe	atc Ile	1371
		Ser							atc Ile							1419
	Val					Trp			tac Tyr						gag Glu 360	. 1467
									cga Arg 370							1515
		_		Thr	_	_	_		ctc Leu				_		_	1563
aag	gtg	atc	tca	gtc	att	gga	ggc	ctg	gcc	gcc	tgc	ttc	atc	ttc	gtc	1611

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gcc Ala	aag Lys	agc Ser	gat Asp	gtg Val 525	ccc Pro	atc Ile	cag Gln	ctg Leu	ctc Leu 530	agc Ser	gcc Ala	acc Thr	aac Asn	cag Gln 535	ttc Phe	2837
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cta Lev	a cgc 1 Arg 410	[ Glu	g cgg L Arg	ctg Leu	gag Glu	cag Gln 415	Glu	cgg Arg	gcc	gag Glu	ctg Leu 420	Glu	cgc Arg	cag Glr	cgc Arg	2501

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ggg ccc ( Gly Pro 1 105									1589
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gcc gag a									1733

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	_				g ttg ctg ctg u Leu Leu Leu	10605
	Gln Asp I		Leu Leu		g gaa gag aag n Glu Glu Lys 3475	10653
-	-				c ctg ctg cag u Leu Leu Gln 3490	10701
Pro Gln Glu		ro Gly Arg			g aca tcc ttt u Thr Ser Phe 3505	10749
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	ctg Leu		Gln					Ala					Ala			9741
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	cgc Arg					Trp					Gln					9837
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gte Val	g cta L Lei	a gco	c cag a Glr	ctg Lev 3080	ı Glı	g gca n Ala	gtt Val	cgg L Arg	g gag g Glu 308!	ı Ala	c ca a Hi	c gca s Ala	a gaq a Gli	g cto u Leo 3090	g ctg 1 Leu )	9501
cg:	g agg	g gcg	g gag a Glu 3099	ı Ala	agg Arg	9 GJ/ 8 GG/	g cad / His	ggo Gly 310	y Lei	g caq u Gli	g ga n Gl	g cag u Gl	g cte n Le 310	u Gl	g cta n Leu	9549
ca	c cag	g ct	g gaç	g cga	a ga	gaco	cte	gct	c ct	c ga	c gc	c tg	g ct	g ac	c acc	9597

***	, 01,5	J <b>4</b> J /												•	CI/OS	01/02023
Glu	Asp	Ser		Ala 600	Ser	Glu	Gly		Trp 2605	Asp	Pro	Leu		Pro 2610	Met	
		Leu				cac His	Lys					Asp				8109
	Ala					gct Ala 2					Āla					8157
Gln					Glu	gcc Ala 2650	_	_	_	Leu			_	-	_	8205
				Lys		gcg Ala			Arg					Arg		8253
			Glu			cgg Arg		Leu					Gln			8301
		Val				ctg Leu	Arg					Val				8349
	Gly					gcc Ala 2					Gln					8397
Gln			_		Glu	ctg Leu 2730	_		_	Met			_	_		8445
ctg Leu 2740	cag Gln	cgg Arg	gag Glu	Gly	cag Gln 2745	agg Arg	ctg Leu	ctg Leu	Gln	ggg Gly 2750	ggc Gly	cac His	cca Pro	Ala	tcg Ser 2755	8493
			Gln			ctg Leu		Glu					Trp			8541
		Asp				aag Lys	Lys					Gln				8589
	Ala					cgg Arg 2					Leu					8637
Glu	ecc Pro 805	atc Ile	gag Glu	gtt Val	Glu	ctg Leu 1810	aga Arg	gcc Ala	ccc Pro	Thr	gtg Val 815	ggc	cag Gln	gcc Ala	ctg Leu	8685
cct Pro 2820	999 Gly	gtg Val	ggc Gly	Glu	ctc Leu 825	ctg Leu	ggc Gly	aca Thr	Gln	agg Arg 830	gag Glu	ctg Leu	gag Glu	Ala	gca Ala 835	8733
gtg Val	gac Asp	aag Lys	Lys	gcc Ala 840	agg Arg	cag Gln	gct Ala	Glu	gca Ala 845	ctg Leu	ctg Leu	ggc Gly	Gln	gcc Ala 850	gag Glu	8781
gcc	ttt	gtg	agg	gaa	ggc	cac	tgc	ctt	gcc	cga	gat	gtg	gaa	gag	cag	8829

VV.	U 01/.	33437													PC17U	801/02623
Ser 2340	Gln	Leu	Asn		Arg 2345	Trp	Ala	Ser		His 2350	Gly	Asn	Leu		Arg 2355	
tac Tyr	cag Gln	cag Gln	Gln	ctc Leu 2360	gaa Glu	Gly ggg	gcc Ala	Leu	gag Glu 2365	ata Ile	cac His	gtg Val	Leu	tcc Ser 2370	cga Arg	7341
gag Glu	ctg Leu	gac Asp	aat Asn 2375	gtc Val	acc Thr	aag Lys	Arg	att Ile 2380	cag Gln	gag Glu	aag Lys	Glu	gcc Ala 2385	ctg Leu	atc Ile	7389
cag Gln	Ala	ctg Leu 2390	gac Asp	tgt Cys	gly aaa	Lys	gat Asp 2395	ctg Leu	gag Glu	agc Ser	Val	cag Gln 2400	agg Arg	ctg Leu	ctg Leu	7437
Arg	aaa Lys 2405	cac His	gag Glu	gag Glu	Leu	gag Glu 2410	cgg	gaa Glu	gtg Val	His	ccc Pro 2415	atc Ile	cag Gln	gcc Ala	cag Gln	7485
gtg Val 2420	gag Glu	tcc Ser	cta Leu	Glu	cgt Arg 2425	gaa Glu	gtg Val	ggc Gly	Arg	ctc Leu 2430	tgc Cys	caa Gln	aga Arg	Ser	ccc Pro 2435	7533
gag Glu	gca Ala	gcc Ala	His	ggc Gly 2440	ctc Leu	agg Arg	cac His	Arg	cag Gln 2445	cag Gln	gag Glu	gtg Val	Ala	gag Glu 2450	agc Ser	7581
tgg Trp	tgg Trp	cag Gln	ctc Leu 2455	cgg Arg	agc Ser	agg Arg	Ala	cag Gln 2460	aag Lys	cgg Arg	agg Arg	Glu	gcg Ala 2465	ctg Leu	gat Asp	7629
gcc Ala	Leu	cac His 2470	caa Gln	gct Ala	cag Gln	Lys	ctc Leu 2475	cag Gln	gca Ala	atg Met	Leu	cag Gln 2480	gaa Glu	ttg Leu	ctg Leu	7677
Val :	Ser 2485	gcc Ala	Gln	Arg	Leu	Arg 2490	Ala	Gln	Met	Asp	Thr 2495	Ser	Pro	Āla	Pro	7725
Arg 2500	Ser	cct Pro	Val	Glu	Ala 2505	Arg	Arg	Met	Leu 2	Glu 2510	Glu	His	Gln	Glu	Cys 2515	7773
Lys	Ala	gag Glu	Leu 2	Asp 2520	Ser	Trp	Thr	Asp 2	Ser 2525	Ile	Ser	Leu	Ala 2	Arg 2530	Ser	7821
Thr	Gly		Gln 2535	Leu	Leu	Thr	Ala 2	Gly 2540	His	Pro	Phe	Ser 2	Ser 2545	Asp	Ile	7869
Arg	GIn 2	gtg Val 2550	Leu	Ala	Gly	Leu 2	Glu 2555	Gln	Glu	Leu	Ser	Ser 2560	Leu	Glu	Gly	7917
Ala	tgg Trp 2565	cag Gln	gag Glu	cat His	Gln	cta Leu 570	cag Gln	ctg Leu	cag Gln	Gln	gcc Ala 2575	ctg Leu	gag Glu	cta Leu	cag Gln	7965
2580	Pne	ctg Leu	Ser	Ser 2	Val :585	Glu	Lys	Met	Glu 2	Arg 590	Trp	Leu	Cys	Ser 2	Lys 2595	8013
gaa	gac	tcc	cta	gcc	agt	gag	ggt	cta	tgg	gac	ccc	ttg	gcc	ccc	atg	8061

		Glu 2085		Leu	Ile		Lys 2090		Glu	Val	Phe	Leu 2095		Val	Leu	Thr	
	gcc Ala 2100	Gln	gac Asp	aag Lys	Lys	gag Glu 2105	Ala	gcc Ala	ctg Leu	Arg	gag Glu 2110	Arg	ctg Leu	aag Lys	Thr	ctc Leu 2115	6573
				cgg Arg		Arg			Leu		Ile			Gln			6621
	atg Met	aga Arg	Val	aag Lys 2135	Glu	ctg Leu	gcg Ala	Glu	agc Ser 2140	cgg Arg	gga Gly	cac His	Ala	ctg Leu 2145	cat His	gcc Ala	6669
	tcc Ser	Leu	Ctg Leu 2150	atg Met	gcc Ala	agc Ser	Phe	acc Thr 2155	cag Gln	gcc Ala	gca Ala	Thr	cag Gln 2160	gct Ala	gag Glu	gac Asp	6717
	Trp	atc Ile 2165	Gln	gcg Ala	tgg Trp	Ala	cag Gln 2170	cag Gln	ctg Leu	aag Lys	Glu	ccg Pro 2175	gtc Val	cct Pro	cct Pro	gly ggg	6765
;	gac Asp 2180	ctg Leu	aga Arg	gat Asp	Lys	ctg Leu 2185	aag Lys	ccc Pro	ctg Leu	Leu	aaa Lys 2190	cac His	cag Gln	gcc Ala	Phe	gag Glu 2195	6813
	gct Ala	gaa Glu	gtc Val	cag Gln	gcc Ala 2200	cat His	gag Glu	gag Glu	Val	atg Met 2205	acc Thr	tct Ser	gtt Val	Ala	aag Lys 2210	aag Lys	6861
	gga Gly	gag Glu	Ala	ctc Leu 2215	ctg Leu	gca Ala	cag Gln	Ser	cac His 2220	cct Pro	cga Arg	gcc Ala	Gly	gag Glu 2225	gtc Val	tcc Ser	6909
	cag Gln	Arg	ctg Leu 2230	cag Gln	ggc Gly	ctg Leu	Arg	aag Lys 2235	cac His	tgg Trp	gag Glu	Asp	ctg Leu 2240	agg Arg	cag Gln	gca Ala	6957
	Met	gcc Ala 2245	ctc Leu	agg Arg	ggc Gly	Gln	gag Glu 2250	ctg Leu	gag Glu	gac Asp	Arg	cgg Arg 2255	aac Asn	ttc Phe	ctg Leu	gag Glu	7005
2	ttc Phe 2260	ctg Leu	cag Gln	aga Arg	Val	gac Asp 2265	ctt Leu	gca Ala	gag Glu	Ala	tgg Trp 2270	Ile	cag Gln	gag Glu	Lys	gag Glu 275	7053
	gtg Val	aag Lys	atg Met	aat Asn	gtt Val 2280	ggt Gly	gac Asp	ctg Leu	Gly	cag Gln 285	gac Asp	ctg Leu	gag Glu	His	tgc Cys 290	ctg Leu	7101
	cag Gln	ctc Leu	Arg	cgg Arg 2295	cgg Arg	ctc Leu	cgc Arg	Glu	ttc Phe 300	cga Arg	gga Gly	aac Asn	Ser	gcc Ala 305	gly ggg	gaç Asp	7149
	aca Thr	Val	ggt Gly 2310	gat Asp	gcc Ala	tgc Cys	Ile	agg Arg 315	agc Ser	atc Ile	agt Ser	Asp	ttg Leu 320	tca Ser	ctg Leu	cag Gln	7197
	Leu	aag Lys 325	aac Asn	cgg Arg	gac Asp	Pro	gag Glu 330	gaa Glu	gtc Val	aag Lys	Ile	atc Ile 3335	tgc Cys	cag Gln	cgg Arg	cga Arg	7245
	agc	cag	ctc	aac	aac	agg	tgg	gcg	agt	ttc	cat	ggc	aac	ttg	ctc	cgg	7293

Ala Arg Gly His Ala Leu Arg Asp Thr Glu Thr Thr Leu Arg Val His 1835 aga gat etc ttg gaa gte etc ace cag gte cag gag aaa gee acg age 5805 Arg Asp Leu Leu Glu Val Leu Thr Gln Val Gln Glu Lys Ala Thr Ser 1850 1855 ctc ccc aac aat gtg gca cgg gac ctg tgt ggg ctg gag gcg cag ctg 5853 Leu Pro Asn Asn Val Ala Arg Asp Leu Cys Gly Leu Glu Ala Gln Leu 1865 aga agc cac cag ggg ctg gag cga gaa ctc gtg ggc acc gag cgg cag 5901 Arg Ser His Gln Gly Leu Glu Arg Glu Leu Val Gly Thr Glu Arg Gln 1880 1.885 ctg cag gaa ctg ctg gag act gca ggc agg gtg cag aag ctg tgt ccg 5949 Leu Gln Glu Leu Leu Glu Thr Ala Gly Arg Val Gln Lys Leu Cys Pro 1895 1900 ggg cct cag gcc cat gcg gtg cag cag agg cag caa gct gtg acg cag 5997 Gly Pro Gln Ala His Ala Val Gln Gln Arg Gln Gln Ala Val Thr Gln 1915 geg tgg gea gtg ctg cag cga cgc atg gag cag cgc agg gcc cag ctg 6045 Ala Trp Ala Val Leu Gln Arg Arg Met Glu Gln Arg Arg Ala Gln Leu 1930 gag cgg gca cgc ctc ctg gcc cgc ttc cgc acg gcg gtg cgt gac tat 6093 Glu Arg Ala Arg Leu Leu Ala Arg Phe Arg Thr Ala Val Arg Asp Tyr 1945 1950 gcc tcc tgg gca gcc cgc gtg cgc cag gac ctg cag gtg gag gag agt 6141 Ala Ser Trp Ala Ala Arg Val Arg Gln Asp Leu Gln Val Glu Glu Ser 1960 1965 tog caa gag cot age agt ggc cog ctg aag ctc agt gcc cac cag tgg 6189 Ser Gln Glu Pro Ser Ser Gly Pro Leu Lys Leu Ser Ala His Gln Trp 1975 1980 ctc cgg gcg gag ctg gag gcc cgg gag aag ctg tgg cag cag gcc acc 6237 Leu Arg Ala Glu Leu Glu Ala Arg Glu Lys Leu Trp Gln Gln Ala Thr 1990 1995 cag ctg ggg cag cag gca ctt ctt gct gca ggg aca ccc acc aag gag 6285 Gln Leu Gly Gln Gln Ala Leu Leu Ala Ala Gly Thr Pro Thr Lys Glu gtc cag gaa gag ctt cga gcc ctg cag gac cag cgg gac cag gtg tat 6333 Val Gln Glu Glu Leu Arg Ala Leu Gln Asp Gln Arg Asp Gln Val Tyr 2025 2030 cag acc tgg gca cgg aag caa gag agg ctg cag gcc gag cag cag gag 6381 Gln Thr Trp Ala Arg Lys Gln Glu Arg Leu Gln Ala Glu Gln Glu Gln Glu 2045 cag etc tte etc aga gag tge gge ege etg gag gag atc etc geg gee 6429 Gln Leu Phe Leu Arg Glu Cys Gly Arg Leu Glu Glu Ile Leu Ala Ala 2055 cag gag gtc tcc ctg aaa acc agt gcc ttg ggg agc tcg gtg gaa gag 6477 Gln Glu Val Ser Leu Lys Thr Ser Ala Leu Gly Ser Ser Val Glu Glu 2075 2080 gta gag cag ttg att cgc aag cac gag gtc ttc ctg aag gtt ctg act 6525

His Gln Gly Gln Val Gln Arg Val Leu Ser Ser Gly Arg Ser Leu Ala gcc tca ggg cac ccc caa gcc caa cac atc gtg gag cag tgc cag gag 5037 Ala Ser Gly His Pro Gln Ala Gln His Ile Val Glu Gln Cys Gln Glu 1590 . 1595 ctg gaa ggc cac tgg gca gag ctg gag agg gca tgt gaa gcg cgg gcc 5085 Leu Glu Gly His Trp Ala Glu Leu Glu Arg Ala Cys Glu Ala Arg Ala 1610 cag tgt ctg cag cag gct gtc act ttc cag cag tac ttt ctg gat gtg 5133 Gln Cys Leu Gln Gln Ala Val Thr Phe Gln Gln Tyr Phe Leu Asp Val 1625 1630 tca gag ctg gag ggc tgg gtg gag gag aag cgg ccg ctg gtg agc agt 5181 Ser Glu Leu Glu Gly Trp Val Glu Glu Lys Arg Pro Leu Val Ser Ser 1640 1645 egg gac tat ggc aga gac gag gca gcc acc ctc agg ctc att aac aag 5229 Arg Asp Tyr Gly Arg Asp Glu Ala Ala Thr Leu Arg Leu Ile Asn Lys 1660 cac cag gct cta cag gag gaa cta gcc att tac tgg agc tcc atg gag 5277 His Gln Ala Leu Gln Glu Glu Leu Ala Ile Tyr Trp Ser Ser Met Glu 1670 1675 1680 gag ett gac cag acg gec caa acc etc act ggc eec gaa gte eet gag 5325 Glu Leu Asp Gln Thr Ala Gln Thr Leu Thr Gly Pro Glu Val Pro Glu 1685 1690 cag cag cgt gtg gtg cag gag agg ctc cgg gag cag ctg cgg gca ctg 5373 Gln Gln Arg Val Val Gln Glu Arg Leu Arg Glu Gln Leu Arg Ala Leu 1705 1710 cag gag ttg gcg gcc aca cgg gac cgg gaa ctg gag ggg acc ctg agg 5421 Gln Glu Leu Ala Ala Thr Arg Asp Arg Glu Leu Glu Gly Thr Leu Arg 1720 1725 ctg cat gag ttc ctg agg gag gct gag gac ctg cag ggc tgg ctg gca 5469 Leu His Glu Phe Leu Arg Glu Ala Glu Asp Leu Gln Gly Trp Leu Ala 1735 1740 age cag aag cag gea gee aaa gga ggg gag age etg gga gag gac eec 5517 Ser Gln Lys Gln Ala Ala Lys Gly Glu Ser Leu Gly Glu Asp Pro 1750 1755 gag cac gcc ctg cac ctc tgc acc aag ttt gca aag ttt cag cac caa 5565 Glu His Ala Leu His Leu Cys Thr Lys Phe Ala Lys Phe Gln His Gln 1765 1770 gtg gag atg ggc agc cag cgg gtg gcc gcc tgc cgg ctg ctg gcg gag 5613 Val Glu Met Gly Ser Gln Arg Val Ala Ala Cys Arg Leu Leu Ala Glu 1780 1785 age etg eta gag egt ggg eac agt get gge eec atg gte egt eag agg 5661 Ser Leu Leu Glu Arg Gly His Ser Ala Gly Pro Met Val Arg Gln Arg 1800 1805 cag cag gat ctg cag acc gcc tgg tcg gag ctg tgg gag ctg acc cag 5709 Gln Gln Asp Leu Gln Thr Ala Trp Ser Glu Leu Trp Glu Leu Thr Gln 1820 gcc cga ggc cac gcg ctc cga gac acc gag acc acc ctc aga gtt cac

Leu Gln Glu Trp Lys Gln Asp Val Ala Glu Leu Met Gln Trp Met Glu . 1325 gag aag ggg ctg atg gct gcg cat gag ccc tcc gga gcg cgc aga aac 4269 Glu Lys Gly Leu Met Ala Ala His Glu Pro Ser Gly Ala Arg Arg Asn 1340 1335 atc ctg cag aca ctc aag cgg cac gaa gca gct gag agc gag cta ctc 4317 Ile Leu Gln Thr Leu Lys Arg His Glu Ala Ala Glu Ser Glu Leu Leu 1355 1350 gcc acc cgc aga cac gtg gag gcc ctg cag cag gtt ggg aga gag ctg 4365 Ala Thr Arg Arg His Val Glu Ala Leu Gln Gln Val Gly Arg Glu Leu 1365 1370 ttg agt agg agg ccc tgt ggc cag gag gac ata cag acc agg ctt caa 4413 Leu Ser Arg Arg Pro Cys Gly Gln Glu Asp Ile Gln Thr Arg Leu Gln 1380 1385 1390 ggc ctg aga agc aag tgg gaa gct ttg aac cgc aag atg act gag cgt 4461 Gly Leu Arg Ser Lys Trp Glu Ala Leu Asn Arg Lys Met Thr Glu Arg 1400 1405 ggg gac gag ctc cag cag gct gga cag cag gag caa ctc ctg agg cag 4509 Gly Asp Glu Leu Gln Gln Ala Gly Gln Glu Gln Leu Leu Arg Gln 1420 ctg cag gat gca aag gag cag ctg gag cag ctc gaa ggg gcc cta cag 4557 Leu Gln Asp Ala Lys Glu Gln Leu Glu Gln Leu Glu Gly Ala Leu Gln 1430 1435 1440 age teg gaa aca ggg cag gae etg ege tee age cag agg etg cag aaa 4605 Ser Ser Glu Thr Gly Gln Asp Leu Arg Ser Ser Gln Arg Leu Gln Lys egg cae caa cag etg gag agt gag age egg ace etg get gee aag atg 4653 Arg His Gln Gln Leu Glu Ser Glu Ser Arg Thr Leu Ala Ala Lys Met 1460 1465 .1470 get ged etc ged ted atg ged cat ggd atg ged ged ted deg ged atc 4701 Ala Ala Leu Ala Ser Met Ala His Gly Met Ala Ala Ser Pro Ala Ile 1480 1485 ctg gaa gag acc cag aag cac ctc cgg agg ctg gag ctt ctg cag ggg 4749 Leu Glu Glu Thr Gln Lys His Leu Arg Arg Leu Glu Leu Leu Gln Gly 1500 cat ctg gcc atc cgg ggc ctg cag ctg cag gcc tca gtg gag ctg cac 4797 His Leu Ala Ile Arg Gly Leu Gln Leu Gln Ala Ser Val Glu Leu His 1515 cag tto tgc cac ctg ago aac atg gag ctc tot tgg gta gcc gag cac 4845 Gln Phe Cys His Leu Ser Asn Met Glu Leu Ser Trp Val Ala Glu His 1530 1535 atg ccc cat ggc agc ccc acc agc tat acc gag tgc ttg aat ggt qcc 4893 Met Pro His Gly Ser Pro Thr Ser Tyr Thr Glu Cys Leu Asn Gly Ala 1540 1555 cag ago ott cac ogo aag cac aag gag oto cag gtg gag gta aaa got 4941 Gln Ser Leu His Arg Lys His Lys Glu Leu Gln Val Glu Val Lys Ala 1560 1565 1570 cac cag ggg cag gtg caa cgg gtg ctg agt tet ggg cgg agc etg gca

Val 1060	Lys	Val	Glu		Pro L065	Gly	Tyr	Ala		Ser 1070	Gln	Pro	Leu		Gly 1075	
			Thr					Leu					gaa Glu			3501
gcc Ala	caa Gln	Arg	gcc Ala 1095	cgg Arg	cgc Arg	cag Gln	Ala	gag Glu 100	act Thr	cag Gln	gcc Ala	Arg	cag Gln 1105	agc Ser	ttc Phe	3549
	Gln					Leu					Glu		gtc Val			3597
Gln					Glu					Val			gct Ala			3645
				His					Glu				ctg Leu	Trp		3693
		_	Gln	-	_	-	-	Gln	_	_		_	gca Ala	_	_	3741
		Pro					Val					Arg	gtc Val L185			3789
	Gln		_		-	Lys	-	-			Gln		cag Gln	-		3837
Leu					Glu					Gly			gtg Val			3885
		_		Cys	_			_	Ala		_		ctg Leu	Āsp		3933
			Asp				_	Leu	-	-	_	-	cag Gln			3981
		Gly					Thr					Ala	gag Glu 1265			4029
cgg Arg	Ala	cac His 1270	ggc Gly	gag Glu	aag Lys	Leu	gtt Val .275	cag Gln	agc Ser	cag Gln	His	cca Pro .280	gct Ala	gca Ala	cac His	4077
Thr					Leu					Ala			acc Thr			4125
				Glu					Gln				tcc Ser	Leu		4173
ctc	cag	gag	tgg	aag	cag	gat	gtg	gca	gag	ctg	atg	cag	tgg	atg	gaa	4221

w	J U1/3	3437												,	rC1/U	301/02023
Leu	Glu 805	Glu	Gln	Gly	Arg	Ala 810	Ala	Ser	Ala	Arg	Ala 815	Ser	Leu	Phe	Thr	
			gcc Ala	_	_					-				Pro		2733
ccc Pro	tgg Trp	agt Ser	gag Glu	gct Ala 840	tcċ Ser	tgc Cys	cac His	cct Pro	ggc Gly 845	cct Pro	gly ggg	gat Asp	gcc Ala	tgg Trp 850	aag Lys	2781
			cca Pro 855													2829
	_		cag Gln			_	_	_								2877
			ctc Leu													2925
ggt Gly 900	ttc Phe	tgc Cys	agt Ser	tcc Ser	tgt Cys 905	gly ggg	gag Glu	ctc Leu	cag Gln	ttg Leu 910	tgg Trp	ctg Leu	gag Glu	aag Lys	cag Gln 915	2973
			ctc Leu													3021
			aaa Lys 935													3069
			gct Ala		-	-	_		-			_		_	_	3117
			aac Asn						_					_	_	3165
	Arg		GJÀ aaa			Glu	Ala	Leu		Arg	Glu					3213
_	_		agt Ser		-	-	_	Ser		_	_	-	Cys			3261
		Val	cag Gln 1015	Leu			Val					Glu				3309
	Gly		tca Ser			Thr					Gln					3357
Lys		Leu	gtg Val		Glu					Phe						3405
gta	aag	gtc	gag	gag	cca	ggc	tac	gca	gag	agc	cag	cct	ctg	caa	gga	3453

***	01,5	3431														
Gln	Leu	Glu 550	Glu	Leu	Gln	Glu	Pro 555	Ala	Arg	Ser	Thr	Ala 560	Сув	Gly	Gln	
cag Gln	ctg Leu 565	gca Ala	gaa Glu	gtg Val	gtg Val	gag Glu 570	ctg Leu	ctg Leu	cag Gln	agg Arg	cat His 575	gac Asp	ctg Leu	ctg Leu	gag Glu	1965
gct Ala 580	caa Gln	gtc Val	tcg Ser	gcc Ala	cac His 585	gga Gly	gcc Ala	cat His	gtg Val	agc Ser 590	cat His	ctt Leu	gct Ala	cag Gln	cag Gln 595	2013
aca Thr	gca Ala	gag Glu	ctg Leu	gac Asp 600	tcc Ser	tcc Ser	ctg Leu	ggc Gly	acc Thr 605	agt Ser	gtg Val	gag Glu	gtg Val	ctg Leu 610	cag Gln	2061
gcc Ala	aag Lys	gcc Ala	agg Arg 615	aca Thr	ctg Leu	gcc Ala	cag Gln	ctc Leu 620	caa Gln	cag Gln	agc Ser	ctg Leu	gtg Val 625	gct Ala	ctt Leu	2109
gtc Val	agg Arg	gcc Ala 630	cgg Arg	cgg Arg	gcc Ala	ctg Leu	ctg Leu 635	gag Glu	cag Gln	acc Thr	ctg Leu	cag Gln 640	cgg Arg	gca Ala	gag Glu	2157
ttc Phe	ctg Leu 645	cgc Arg	aac Asn	tgt Cys	gag Glu	gag Glu 650	gag Glu	gaa Glu	gcc Ala	tgg Trp	ctg Leu 655	aag Lys	gag Glu	tgc Cys	gga Gly	2205
cag Gln 660	cgg Arg	gtg Val	gly ggg	aat Asn	gcg Ala 665	gcc Ala	ctg Leu	ggc Gly	cgg Arg	gat Asp 670	ctc Leu	agc Ser	cag Gln	atc Ile	gca Ala 675	2253
ggc	gcc Ala	ctg Leu	cag Gln	aaa Lys 680	cac His	aag Lys	gcc Ala	ctg Leu	gaa Glu 685	gct Ala	gag Glu	gtc Val	cac His	cgc Arg 690	cac His	2301
					gat Asp											2349
					cag Gln											2397
					ctg Leu											2445
					ctg Leu 745											2493
					ctg Leu											2541
					cag Gln											2589
					gtc Val											2637
ctg	gag	gag	cag	aaa	cgg	gcg	gcc	tcg	gcc	cgg	gcg	tcg	tta	ttc	acg	2685

W	O 01/5	5437												1	PC17U	S01/02623
Arg	Arg	Leu	Thr 295	Lys	Ile	Leu	Leu	Gln 300	Leu	Gln	Glu	Thr	Glu 305	Leu	Leu	
	acc Thr															1197
	aag Lys 325															1245
-	atg Met		_		_	_	-					_		_		1293
	r cca Pro															1341
	rcta rLeu	_		_			-	_		-				-		1389
	: gag : Glu		_			-		_		_	-		_		-	1437
	tgg Trp 405	_		-	-		_	_	_	_	_	-			_	1485
	g ctg 1 Leu )	_			-		-	_		_		_	_	_	_	1533
	ctc Leu												Leu			1581
	aga Arg															1629
	g ctg g Leu		Met		Glu		Gly	Ile								1677
	g gcc 1 Ala 485															1725
	tgg Trp															1773
Gl	g agg n Arg	ctc Leu	ctt Leu	cag Gln 520	cat His	cta Leu	cag Gln	gga Gly	cag Gln 525	agg Arg	aag Lys	cag Gln	gtg Val	gca Ala 530	gac Asp	1821
at Me	g cag : Gln	gct Ala	gtg Val 535	ctg Leu	agc Ser	ctg Leu	ctg Leu	cag Gln 540	gag Glu	gtg Val	gag Glu	gct Ala	gcc Ala 545	tcc Ser	cac His	1869
cag	, ctg	gag	gag	ctg	cag	gag	ccg	gcc	agg	tcc	acc	gcc	tgt	ggg	cag	1917

Met	Asp	Ser	Gln	Tyr 40	Glu	Thr	Gly	His	Ile 45	Arg	Lys	Leu	Gln	Ala 50	Arg	
								ttc Phe 60								429
	_	•		_				aag Lys				_			_	477
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Ser Trp Lys Ala Pro Val Ala Thr Asn Asn Pro Ala Trp Ala Val Gln
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80
85

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Asn Cys Thr Leu Ser Ile Arg Asp Ala Arg Met Ser Asp Ala Gly Arg
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145

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Thr Leu Tyr Pro Ser Gln Pro Ser Asn Pro Leu Val Leu Glu Leu Gln
205

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ata Ile 130	aaa <sup>.</sup> Lys	tgg Trp	aat Asn	tat Tyr	aaa Lys 135	tat Tyr	gac Asp	cag Gln	ctc Leu	tct Ser 140	Val	aac Asn	gtg Val	aca Thr	gcc Ala 145	550

220 225 230

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			atg Met													1541
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			aag Lys													1829
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gato	ccag	ıga c	ctccg	gctt	t cg	ıccga	gccg	r cag	cggg	atc	ccts	ıtgca	icc c	ggcg	rcagcc	2057

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Asn Gly Arg Phe Lys Glu Phe Met Ser Lys His Val His Leu Met Cys 205 210 215
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WO 01/55437	PCT/US01/02623
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tat Tyr	gtc Val 40	tcc Ser	atc Ile	cac His	agc Ser	tct Ser 45	ggc Gly	ttt Phe	cgt Arg	gac Asp	ttc Phe 50	ctg Leu	ctc Leu	aag Lys	cca Pro		377
gag Glu 55	ttg Leu	ctc Leu	cgg Arg	gcc Ala	att Ile 60	gtc Val	gac Asp	tgt Cys	ggc	ttt Phe 65	gag Glu	cat His	ccg Pro	tca Ser	gaa Glu 70		425
gtc Val	cag Gln	cat His	gag Glu	tgc Cys 75	atc Ile	cct Pro	cag Gln	gcc Ala	att Ile 80	ctg Leu	gga Gly	atg Met	gat Asp	gtc Val 85	ctg Leu		473
tgc Cys	cag Gln	gcc Ala	aag Lys 90	tcg Ser	ggc Gly	atg Met	gga Gly	aag Lys 95	aca Thr	gca Ala	gtg Val	ttt Phe	gtc Val 100	ttg Leu	gcc Ala		521
aca Thr	ctg Leu	caa Gln 105	Gln	ctg Leu	gag Glu	cca Pro	gtt Val 110	Thr	GJ A GGG	cag Gln	gtg Val	tct Ser 115	gta Val	ctg Leu	gtg Val		569
atg Met	tgt Cys 120	cac His	act Thr	cgg Arg	gag Glu	ttg Leu 125	gct Ala	ttt Phe	cag Gln	atc Ile	agc Ser 130	aag Lys	gaa Glu	tat Tyr	gag Glu		617
ege Arg 135	, Phe	tct	aaa Lys	tac Tyr	atg Met 140	Pro	aat Asn	gtc Val	aag Lys	gtt Val 145	Ala	gtt Val	ttt Phe	ttt Phe	ggt Gly 150		665
Gl	ctg Leu	tct Ser	ato Jle	aag Lys 155	Lys	gat Asp	gaa Glu	gag Glu	gtg Val	. Leu	aag Lys	aag Lys	aac Asn	tgo Cys 165	Pro		713
cat His	ato Ile	gto Val	gtg Val 170	Gly	act Thr	cca Pro	Gly ggd	cgt Arg 175	, Ile	cta Leu	gcc Ala	ctg Lev	gct Ala 180	Arg	aat Asn		761
aaq Lys	g ago s Ser	Let 185	ı Ası	c cto 1 Leu	aaa Lys	cac His	: att	Lys	a cac s His	ttt Phe	att lle	tto Lev	ı Asp	gaa Glu	tgt Cys		809
ga As <sub>l</sub>	t aag p Lys 200	Met	g ctt t Lei	gaa u Glu	a cag ı Glr	g cto Lev 205	ı Ası	e atg p Met	g cgt	g Arg	g gat g Asp 210	val	cag LGlr	g gaa n Glu	a att u Ile		857
tt Pho 21	e Arg	ate Me	g aco	c ccc r Pro	C Cac His 220	s Glu	g aag 1 Lys	g cas s Gl:	g gto n Val	c ato 1 Met 225	: Met	tto Phe	e Sei	gct Ala	t acc a Thr 230		905

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265 270 275	٠
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aag tot gtg cag cgg tgc att gcc ttg gcc cag cta cta gtg gag cag Lys Ser Val Gln Arg Cys Ile Ala Leu Ala Gln Leu Leu Val Glu Gln 295 300 305 310	1145
aac ttc cca gcc att gcc atc cac cgt ggg atg ccc cag gag gag agg Asn Phe Pro Ala Ile Ala Ile His Arg Gly Met Pro Gln Glu Glu Arg 315 320 325	1193
ctt tct cgg tat cag cag ttt aaa gat ttt caa cga cga att ctt gtg Leu Ser Arg Tyr Gln Gln Phe Lys Asp Phe Gln Arg Arg Ile Leu Val 330 335 340	1241
gct acc aac cta ttt ggc cga ggc atg gac atc gag cgg gtg aac att Ala Thr Asn Leu Phe Gly Arg Gly Met Asp Ile Glu Arg Val Asn Ile 345 350 355	1289
gct ttt aat tat gac atg cct gag gat tct gac acc tac ctg cat cgg Ala Phe Asn Tyr Asp Met Pro Glu Asp Ser Asp Thr Tyr Leu His Arg 360 365 370	1337
gtg gcc aga gca ggc cgg ttt ggc acc aag ggc ttg gct atc aca ttt Val Ala Arg Ala Gly Arg Phe Gly Thr Lys Gly Leu Ala Ile Thr Phe 375 380 385 390	1385
gtg tcc gat gag aat gat gcc aag atc ctc aat gat gtg cag gat cgc Val Ser Asp Glu Asn Asp Ala Lys Ile Leu Asn Asp Val Gln Asp Arg 395 400 405	1433
ttt gag gtc aat att agt gag ctg cct gat gag ata gac atc tcc tcc Phe Glu Val Asn Ile Ser Glu Leu Pro Asp Glu Ile Asp Ile Ser Ser 410 415 420	1481
tac att gaa cag aca cgg tag aa gactcgccca ttttggaatg tgaccgtctg Tyr Ile Glu Gln Thr Arg * 425	1534
teetteagga gaggacacea gggtgggggt gaaggagaca etaetgeeee cacceetgae	1594
agececeace ecatggette catettttge atcaceacea etectgaace eccatttetg	1654
atttgtcaga atttttttt aacaaaacta aaaatgaaac acatgtgtct gtggtatcta	1714

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<211> 1648

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

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<400> 213

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1726

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														aag Lys		377
gag Glu 55	ttg Leu	ctc Leu	cgg Arg	gcc Ala	att Ile 60	gtc Val	gac Asp	tgt Cys	ggc Gly	ttt Phe 65	gag Glu	cat His	ccg Pro	tca Ser	gaa Glu 70	425
														gtc Val 85		473
														ttg Leu		521
														ctg Leu		569
														tat Tyr		617
														ttt Phe		665
					Lys									tgc Cys 165		713
		_		Gly				_	Ile		-	_	_	cga Arg		761
_	_		Asn					Lys			_	_	_	gaa Glu		809
		Met					Asp					Val	_	gaa Glu	_	857
	Arg	_				Glu	_	_	_	_	Met		_	_	acc Thr 230	905
					Arg					Lys					cca Pro	953
				Val					Lys					Gly	ttg Leu	1001
															ctc Leu	1049

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Leu Phe Gly Gly Thr Ser Pr 305 310	ro Ser Pro Glu Glu 315	Gly Leu Gly Asp Glu 320	
ttt gac ctt ata gat cat to Phe Asp Leu Ile Asp His Se 325		3 3	186
agt ctg aag act ctg tgc aa Ser Leu Lys Thr Leu Cys Ly 340			234
cag tcc tgt ttg cct cat ga Gln Ser Cys Leu Pro His As 355			282
acc aac agc aat atc agt co Thr Asn Ser Asn Ile Ser An 370	-		330
gaagtttetg ecaceteece teet	tgageet getgteatet	tcactgcccc tgcccatctg 13	390
teacceacet geteetttga ecce	ctggact tggtatacct	ccatgtggag ttgttgggcg 14	450
agaggtgttc tctgtgctgt gaat	ttcagtg gggagctgta	gcggggtggg ggctaggttc 19	510
ctccccctt gggccgaggg cccc	cttcccc ttgggtgctc	tgtccccatc cacctccttt 1	570
cagetgetee tgggeeteag ette	ctgccca gggccagccc	aggttctgct gggaagggaa 10	630
gggaatgggg agaaagggag aag	caagcag tgtctgagcc	tcaggaaget teceeteece 16	690
cttgcctatc ccctcccctc tgct	ttgagee ttgageettg	actgggagct gaaaggagtt 1	750
gcagetgttg gcatgagace teet	tteteee egtettgggg	aggtggggac cagcagataa 18	810
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aaaaaaaaa a		. 18	881

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WO	01/5	5437												ŀ	PCT/US	801/02623
Phe	Asn 50	Ala	Val	Ser	Leu	Arg 55	Trp	Thr	Lys	Leu	Pro 60	Pro	Val	Lys	Ser	
gcc Ala 65	atc Ile	cgt Arg	GJA aaa	caa Gln	gct Ala 70	Pro	gtg Val	gta Val	ccc Pro	tac Tyr 75	atg Met	cgc Arg	tat Tyr	gga Gly	cac His 80	418
tca Ser	acc Thr	gtc Val	ctc Leu	atc Ile 85	gac Asp	gac Asp	aca Thr	gtc Val	ctc Leu 90	ctt Leu	tgg Trp	ggc Gly	gl <sup>à</sup> aaa	cgg Arg 95	aat Asn	466
gac Asp	acc Thr	gaa Glu	ggg Gly 100	gcc Ala	tgc Cys	aat Asn	gtg Val	ctc Leu 105	tat Tyr	gcc Ala	ttt Phe	gac Asp	gtc Val 110	aat Asn	acg Thr	514
cac His	aag Lys	tgg Trp 115	ttc Phe	aca Thr	ccc Pro	cga Arg	gtg Val 120	tca Ser	gly aaa	aca Thr	gtt Val	cct Pro 125	gly aaa	gcc Ala	cgg Arg	562
gat Asp	gga Gly 130	cat His	tca Ser	gcc Ala	tgt Cys	gtc Val 135	cta Leu	ggc Gly	aag Lys	atc Ile	atg Met 140	tac Tyr	att Ile	ttt Phe	gjå aaa	610
ggc Gly 145	tac Tyr	gag Glu	cag Gln	cag Gln	gcg Ala 150	gac Asp	tgt Cys	ttt Phe	tcc Ser	aat Asn 155	gac Asp	att Ile	cac His	aag Lys	cta Leu 160	658
gat Asp	acc Thr	agc Ser	acc Thr	atg Met 165	aca Thr	tgg Trp	act Thr	ctt Leu	atc Ile 170	tgt Cys	aca Thr	aag Lys	ggc	agc Ser 175	cct Pro	706
gca Ala	cgc Arg	tgg Trp	agg Arg 180	gac Asp	ttc Phe	cac His	tca Ser	gcc Ala 185	aca Thr	atg Met	ctg Leu	gga Gly	agt Ser 190	His	atg Met	754
tat Tyr	gtc Val	ttt Phe 195	Gly	ggc Gly	cgt Arg	gcc Ala	gac Asp 200	Arg	ttt Phe	Gly	cca Pro	Phe 205	His	tcc Ser	aac Asn	802
		Ile					Ile					Thr			gag Glu	850
gct Ala 225	tgg Trp	ctg Leu	gac Asp	tgt Cys	Pro 230	Pro	act Thr	cca Pro	gtg Val	ctg Leu 235	Pro	gag Glu	ggg Gly	cgc Arg	cgg Arg 240	898
					Gly					Leu					ggt Gly	946
				Leu					His					Phe	aat Asn	994
			Phe				_	Ile	-	_	_		Lys		cca Pro	1042
		Arg					Cys					Asp			gtc Val	1090
ctc	ttt	ggg	ggt	acc	agt	сса	tct	cct	gag	gaa	ggo	ctg	gga	gat	gaa	1138

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95	100	105	110
aag ccc cgg gcc cca Lys Pro Arg Ala Pro 115	gga gat gag gaa gcc Gly Asp Glu Glu Ala 120	cag gtg gag aac ct Gln Val Glu Asn Le 12	u Ile
	gag ccc cag aaa gca Glu Pro Gln Lys Ala 135		gcca 554
tcaggtggaa gcctctgg	aa cctgaggcgg ctgctt	gaac ctttggatgc aaa	tgtcgat 614
gcttaagaaa accggcca	ct tcagcaacag cccttt	cccc aggagaagcc aag	aacttgt 674
gtgtccccca ccctatcc	cc tctaacacca ttcctc	cacc tgatgatgca act	aacactt 734
gcctccccac tgcagcct	gc ggtcctgccc acctcc	cgtg atgtgtgtgt gtg	tgtgtgt 794
gtgtgtgact gtgtgtgt	tt gctaactgtg gtcttt	gtgg ctacttgttt gtg	gatggta 854
ttgtgtttgt tagtgaac	tg tggactcgct ttccca	ggca ggggctgagc cac	atggcca 914

totgotocte cotgococtg tgggccctcc atcacettet getectagga ggctgcttgt

tgcccgagaa ccagcccct cccntgattt taggggatgg cgtaggggta aggagcaagg

ggcagtggtn ttcaagtngt tttnggtt

<210> 211

974

1034

1062

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aga ggt gac Arg Gly Asp	 	_	_	_				_		_	1208	

tcc gtc agc aga gcc cca agt cca ccg gaa cat tca ctc cca tgg gct 1256 Ser Val Ser Arg Ala Pro Ser Pro Pro Glu His Ser Leu Pro Trp Ala 310 315 320

tcg gag caa cct tca aga gat ctt tct acc tgc ctt tcc atg tca tga 1304 Ser Glu Gln Pro Ser Arg Asp Leu Ser Thr Cys Leu Ser Met Ser 325 330 335

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acacatgtgg atcctcgttt tccaagaaaa aaaaaa 1400

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<221> misc\_feature

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tacagac atg aaa gta agg cgg gga agc agc tca agc ctc acc cac cgc Met Lys Val Arg Arg Gly Ser Ser Ser Ser Leu Thr His Arg

cct gcc ccc agc ccc gcc act ccc agg ctc ctc ggg act cgg gtc

Pro Ala Pro Ser Pro Ala Thr Pro Arg Leu Leu Gly Thr Arg Arg Val

15 20 25 30

ctc ctg gga gtc tcg gag ggg acc ggc tgt gca gac gcc atg gag ttg 265 Leu Leu Gly Val Ser Glu Gly Thr Gly Cys Ala Asp Ala Met Glu Leu 35 40 45

gtg ctg gtc ttc ctc tgc agc ctg ctg gcc ccc atg gtc ctg gcc agt
Val Leu Val Phe Leu Cys Ser Leu Leu Ala Pro Met Val Leu Ala Ser

50
55
60

gca gct gaa aag gag aag gaa atg gac cct ttt cat tat gat tac cag
Ala Ala Glu Lys Glu Met Asp Pro Phe His Tyr Asp Tyr Gln
65 70 75

acc ctg agg att ggg gga ctg gtg ttc gct gtg gtc ctc ttc tcg gtt

Thr Leu Arg Ile Gly Gly Leu Val Phe Ala Val Val Leu Phe Ser Val

80 85 90

ggg atc ctc ctt atc cta agt cgc agg tgc aag tgc agt ttc aat cag 457 Gly Ile Leu Leu Ile Leu Ser Arg Arg Cys Lys Cys Ser Phe Asn Gln

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					ttt Phe											440
				Leu	ctt Leu											488
ttc Phe	att Ile	gtc Val 70	ctg Leu	cac His	ctg Leu	gtc Val	ttg Leu 75	caa Gln	Gly aaa	atg Met	gtt Val	tat Tyr 80	act Thr	gag Glu	tac Tyr	536
		_	_		ggc Gly		_	-	-					_		584
					tat Tyr 105											632
					acc Thr											680
					gtt Val											728
					act Thr											776
	-	_		_	aac Asn		_			_		-			_	824
_					tgc Cys 185			_								872
		-	_		ttg Leu	-	_	_	-	-		-	-			920
					gtc Val											968
				-	gac Asp						-	-	-	_	-	1016
					ctg Leu		_						-		-	1064
					gtt Val 265											1112
					gcg Ala											1160

WO 01/55437 PCT/US01/02623 ecc cet tgg gaa tgg ggt agt gag gee eea gae tte acc eec age eea 1211 Pro Pro Trp Glu Trp Gly Ser Glu Ala Pro Asp Phe Thr Pro Ser Pro 370 ctg cta aaa tct gtt ttc tga ca gatgggtttt ggggagtcgc ctgctgcact 1264 Leu Leu Lys Ser Val Phe \* 385 acatgagaaa gggacteeca tttgecette cettteteet acagteeett ttgtettgte 1324 tgtcctgggc tgtctgtgtg tgtgccattc tctggacttc agagccccct gagccagtcc 1384 tecettecca geetecettt gggeeteeet aactecaect aggetgecag ggaeeggagt 1444 cagetggtte aaggecateg ggagetetge etceaagtet accetteeet teeeggacte 1504 cetectgtee cetectttee tecetectte ettecaetet cettectttt qettecetqe 1564 cettteccce tecteaggtt ettecctect teteactggt ttttecacet tecteettee 1624 cttcttccct ggctcctagg ctgtgatata tatttttgta ttatctcttt ottcttcttg 1684 tggtgatcat cttgaattac tgtgggatgt aagtttcaaa attttcaaat aaagcctttg 1744

1763

caagataaaa aaaaaaaaa

<210> 209 <211> 1400 <212> DNA

<213> Homo sapiens

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											tct Ser					443
	_	_				-					ctc Leu	-				491
											gly aaa					539
											999 Gly 170					587
											atc Ile					635
											tgc Cys					683
								_			gcc Ala	_		_		731
											gct Ala					779
											cct Pro 250					827
ccc Pro 255	cga Arg	GJ y ggg	gga Gly	ccc Pro	cgg Arg 260	cct Pro	gjå aaa	atg Met	ccc Pro	cac His 265	ccc Pro	aag Lys	gjà aaa	gct Ala	cca Pro 270	875
gcc Ala	ttc Phe	cag Gln	ttg Leu	aac Asn 275	cgc Arg	tca Ser	ctc Leu	agt Ser	ggt Gly 280	cag Gln	cgt Arg	ttc Phe	ctg Leu	cac His 285	act Thr	923
tta Leu	cct Pro	ctc Leu	atg Met 290	tgc Cys	gtt Val	tcc Ser	cgg Arg	cct Pro 295	gat Asp	gtt Val	gtg Val	gtg Val	gtg Val 300	tgc Cys	ggc Gly	971
gtg Val	ctc Leu	act Thr 305	ctc Leu	tcc Ser	ctc Leu	atg Met	aac Asn 310	acc Thr	cac His	cca Pro	cct Pro	cgt Arg 315	ttc Phe	cgc Arg	agc Ser	1019
ccc Pro	tgc Cys 320	atg Met	ctg Leu	ctc Leu	cag Gln	agg Arg 325	tgg Trp	gtg Val	gga Gly	ggt Gly	gag Glu 330	ctg Leu	gly ggg	gct Ala	cct Pro	1067
tgg Trp 335	gcc Ala	ctc Leu	atc Ile	ggt Gly	cat His 340	ggt Gly	ctc Leu	gtc Val	cca Pro	ttc Phe 345	cac His	acc Thr	att Ile	tgt Cys	ttc Phe 350	1115
tct Ser	gtc Val	tcc Ser	cca Pro	tcc Ser 355	tac Tyr	tcc Ser	aag Lys	gat Asp	gcc Ala 360	ggc Gly	atc Ile	acc Thr	ctg Leu	agg Arg 365	gct Ala	1163

acg tgg tgt gaa ctg aga ggt gat gag atg Thr Trp Cys Glu Leu Arg Gly Asp Glu Met 30 35	cgt aga tca tct gcc ccc 509 Arg Arg Ser Ser Ala Pro 40
tgc ctg gtg ggc agc cct ggc ccc acg tgc Cys Leu Val Gly Ser Pro Gly Pro Thr Cys 45 50	tga cccaggca cagaaaagcc 560 *
acatacgtgt actgggcacg ctctatggaa gaacggt	gaa ttgttgctct ggcaaataat 620
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gaa	. 863

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Met Glu Ser Arg Met Trp Pro Ala Leu Leu Leu Ser His Leu

1 5 10

ctc cct ctc tgg cca ctg ctg ttg ctg ccc ctc cca ccg cct gct cag 155

Leu Pro Leu Trp Pro Leu Leu Leu Leu Pro Leu Pro Pro Pro Ala Gln
15 20 25 30

gac tot toa toe toe cet ega acc cea cea gee cea gee ege cec ceg
Asp Ser Ser Ser Pro Arg Thr Pro Pro Ala Pro Ala Arg Pro Pro
35 40 45

tgt gcc agg gga ggc ccc tcg gcc cca cgt cat gtg tgc gtg tgg gag 251 Cys Ala Arg Gly Gly Pro Ser Ala Pro Arg His Val Cys Val Trp Glu 50 55 60

cga gca cct cca cca agc cga tct cct cgg gtc cca aga tca cgt cgg 299
Arg Ala Pro Pro Pro Ser Arg Ser Pro Arg Val Pro Arg Ser Arg Arg
65 70 75

caa gtc ctg cct ggc act gca ccc cca gcc acc cca tca ggc ttt gag

Gln Val Leu Pro Gly Thr Ala Pro Pro Ala Thr Pro Ser Gly Phe Glu

85

90

gag ggg ccg ccc tca tcc caa tac ccc tgg gct atc gtg tgg ggt ccc
Glu Gly Pro Pro Ser Ser Gln Tyr Pro Trp Ala Ile Val Trp Gly Pro
95 100 105 110

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Tyr Tyr Phe Leu Ser Leu Ser Asn Ile Phe Ile Leu Thr Ile Gly Leu  10 15 20	100
acg tgt gcc tct ggc ccc ctt gac ttt acc cct gtg ttt ctg ctt gga Thr Cys Ala Ser Gly Pro Leu Asp Phe Thr Pro Val Phe Leu Leu Gly 25 30 35 40	148
aag ggc tcc ctg aag tgc aaa tat ggt cct gtt gca cat ttg ccc cct Lys Gly Ser Leu Lys Cys Lys Tyr Gly Pro Val Ala His Leu Pro Pro 45 50 55	196
gaa gct ctg gaa agc ggt ccc caa atc cca tcc gga tgt aac tgg aag Glu Ala Leu Glu Ser Gly Pro Gln Ile Pro Ser Gly Cys Asn Trp Lys 60 65 70	244
gaa att cca aca tcc tcc tag tc cagccgaggg ggttcccacc acggatttcc Glu Ile Pro Thr Ser Ser * 75	297
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agaattetee gtgtgteatt tttetgtagt tecatttaat geagtgatag ttattttta	417
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tgc aag ttg ctt ctt ctg act aga gtc tgc tac Cys Lys Leu Leu Leu Thr Arg Val Cys Tyr 5 10 15	ctg atc acc ccg tta Leu Ile Thr Pro Leu 20	283
gat ctt gag agg ttt ccc ttc cca aac act gag Asp Leu Glu Arg Phe Pro Phe Pro Asn Thr Glu 25 30		331
gaa cgc aga gtt agc gtc ttc ctg ctg cct ctg Glu Arg Arg Val Ser Val Phe Leu Leu Pro Leu 40 45	agc tgg tgt ttg gac Ser Trp Cys Leu Asp 50	379
aca agg ctg ccc aga gag cct ggc tgc agg tgt Thr Arg Leu Pro Arg Glu Pro Gly Cys Arg Cys 55 60	cga cac agc tct cca Arg His Ser Ser Pro 65	42
cag gac gtg gtt ggc ggc agt cac ctg gtc acc Gln Asp Val Val Gly Gly Ser His Leu Val Thr 70 75	aca act ctt cta agc Thr Thr Leu Leu Ser 80	475
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aat tat gta tgt tgg aaa ctg gtc tct agc cct aga ctt gga caa aag Asn Tyr Val Cys Trp Lys Leu Val Ser Ser Pro Arg Leu Gly Gln Lys 70 75 80	775
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tta atg gtt ttg aaa tta gtg att tgc tct att ttc att gga aag gaa Leu Met Val Leu Lys Leu Val Ile Cys Ser Ile Phe Ile Gly Lys Glu 5 . 10 . 15	225
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gat act ctt aag tca gtt cat cag cca tgc agt gca ctg tct ggt tat Asp Thr Leu Lys Ser Val His Gln Pro Cys Ser Ala Leu Ser Gly Tyr 35 40 45	321
aac atg cct gaa aag cca gag gaa tgt tct atc aaa gag cgg cat ccc Asn Met Pro Glu Lys Pro Glu Glu Cys Ser Ile Lys Glu Arg His Pro 50 55 60 65	369
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30

631

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Leu Met Gly Val Thr Ala Lys Thr Lys Val Lys Pro Leu Leu Pro Arg

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tgc tat aaa tgt aga tac att tct ttc tcc ttt aca ttt tcc gtc aca Cys Tyr Lys Cys Arg Tyr Ile Ser Phe Ser Phe Thr Phe Ser Val Thr 35 40 45	205

253

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730

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ctactcatct tttcagctgg tttttcattt	gattttatac	catttcctca c atg cat Met His 1	237
gta ctg atc aga act ccc tgc tct val Leu Ile Arg Thr Pro Cys Ser 10	cta ata ctc Leu Ile Leu	tgc ctg gca aac tct Cys Leu Ala Asn Ser 15	285
agc cac gct agt cta cct gga ttc Ser His Ala Ser Leu Pro Gly Phe 20 25			333
gag tot tgc aga ctc ctt ctg aat Glu Ser Cys Arg Leu Leu Leu Asn 35 40	tct tcc ttt Ser Ser Phe 45	ctg ctg cat ggc cta Leu Leu His Gly Leu 50	381
gaa att ctc tca ggg gca att gca Glu Ile Leu Ser Gly Ala Ile Ala 55	ggc aaa tgc Gly Lys Cys 60	aac tca ttt tgt ttg Asn Ser Phe Cys Leu 65	429
ttt tcc atc tct cag gga tca ctg Phe Ser Ile Ser Gln Gly Ser Leu 70			477
cct tga aaaccattgt ttaatatatt ca Pro *	tetggaet tti	taggtgtg ggcattggaa	533
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 $\langle 223 \rangle$  n = a,t,c or g

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ctc cct cac aac atc ccg tcc agc ctg agc ctg ctc acc agc atg gtg Leu Pro His Asn Ile Pro Ser Ser Leu Ser Leu Leu Thr Ser Met Val 210 215 220	731
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tac acc cgc cga gcc atg ctg gct gcc atc tac aac aca aca gag ctg Tyr Thr Arg Arg Ala Met Leu Ala Ala Ile Tyr Asn Thr Thr Glu Leu 245 250 255	827
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attactggaa gacagtgtaa taggcttg atg tct gtc ctc atc tgg tgt ttg 232
Met Ser Val Leu Ile Trp Cys Leu

ata ttc ttt cct ctt gag tat tcc agg ccc aag aga ggc ttg aaa gtt 280

Ile Phe Phe Pro Leu Glu Tyr Ser Arg Pro Lys Arg Gly Leu Lys Val

10 15 20

gat aat gtg tgt ttt tcc act gtt gcc ctt tca aca ggg tct aga att
Asp Asn Val Cys Phe Ser Thr Val Ala Leu Ser Thr Gly Ser Arg Ile
25 30 35 40

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Ser Asn Trp Ser Asn Cys Glu Thr Cys Leu Leu Ala Glu Met Phe Phe
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ctt gat ttg ggg ttt tct tga aa ttattgccaa agtcatatga cataaattgt 429 Leu Asp Leu Gly Phe Ser \*

489

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caatccctgc gtcaatgatt aataaaaaca ctctagcctg agggtgggct tgtgctgaaa 669

gct gag cca aga gca gat ggc agc cgc cgg act aca cgc tat gac att Ala Glu Pro Arg Ala Asp Gly Ser Arg Arg Thr Thr Arg Tyr Asp Ile 135 140 145	489
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gtt gac gct atc gtg gag ggc ccc aac ttt gag ttc tcc acc gag acg Val Asp Ala Ile Val Glu Gly Pro Asn Phe Glu Phe Ser Thr Glu Thr 165 170 175	585
cat gag gag ttg ctg tac aac aag gag aag cta ctc aac aat ggt gac His Glu Glu Leu Leu Tyr Asn Lys Glu Lys Leu Leu Asn Asn Gly Asp 180 185 190 195	633
aag tgg gag gcc gag atc gcg gcc aac atc cag gct gac tac ctg tat Lys Trp Glu Ala Glu Ile Ala Ala Asn Ile Gln Ala Asp Tyr Leu Tyr 200 205 210	681
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gag Glu	gat Asp 75	ctg Leu	ctt Leu	tgc Cys	tgt Cys	tac Tyr 80	tct Ser	tcc Ser	atg Met	gtc Val	tct Ser 85	cgg Arg	aag Lys	aac Asn	aaa Lys	472
atc Ile 90	agg Arg	cgc Arg	aat Asn	cgg Arg	cag Gln 95	cta Leu	gag Glu	agg Arg	ctg Leu	gct Ala 100	tcc Ser	cac His	atc Ile	aag Lys	gaa Glu 105	520
ctg Leu	gag Glu	ccc Pro	aag Lys	ctg Leu 110	aag Lys	aag Lys	att Ile	ctg Leu	cag Gln 115	atg Met	aac Asn	cca Pro	agg Arg	atg Met 120	cgg Arg	568
aag Lys	ttc Phe	caa Gln	gtg Val 125	gat Asp	atg Met	acc Thr	ttg Leu	gat Asp 130	gcc Ala	aac Asn	aca Thr	gcc Ala	aac Asn 135	aac Asn	ttc Phe	616
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His	Arg	Lys	999 Gly 205	Arg	Ile	Gln	Leu	Thr 210	Thr	Glu	Leu	Gly	Phe 215	Trp	Thr	856
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act Thr	tto Phe 235	Lev	tto Phe	gta Val	gac Asp	cgc Arg 240	Lys	tta Leu	cag Gln	cga Arg	gtg Val 245	Gly	att Ile	ttt Phe	ctg Leu	952
gat Asr 250	Met	ggq Gly	atg / Met	cag Gln	aac Asn 255	Val	tco Ser	ttt Phe	ttt Phe	gat Asp 260	Ala	gaa Glu	ggt Gly	ggt	tcc Ser 265	1000
cat His	t gto s Val	tat Tyi	aca Thr	tto Phe	Arg	ago Ser	gta Val	tct Ser	gct Ala 275	Glu	gag Glu	, cca . Pro	ctg Leu	tgo Cys 280	cca Pro	1048
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1458

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70

Ala Val Cys Leu Lys Cys Ile Asn Ser Leu Gln Lys Glu Pro His Gly

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								ctt Leu								196
_	_					-		tct Ser					_			244
			_	-			-	gca Ala	-						-	292
_		_	_	-		-	_	cag Gln	-			_		_		340
	_		_		•		_	ggt Gly 115		_				_	-	388
		_						tcc Ser	_	_			_		_	. 436
								aga Arg								484
	_					_		tat Tyr			_	_	_			532
								cag Gln								580
	_	-		_	_		_	tct Ser 195				Leu		_		628
								tgc Cys								676
								aaa Lys								724
								gaa Glu								772
								ttc Phe								820
_		-	_		-			tac Tyr 275	_		_			_		868

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WO 01/55437

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1257

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_	-			aat Asn 155	_			_		_		-	_			534
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				gtg Val												630
				gct Ala												678
				ggc Gly	_									_		726
				ggc Gly 235												774
	_	_		gcc Ala		_	_			_		_	_	-		822
				cgg Arg												870
_		Gln	-	aac Asn	_	_	-	_	_	_			_	_	-	918
	Ala			gjà aaa		_	-		_		_	_		_		966
				gtg Val 315												1014
	-			gct	-			_	_		_	_			-	1062
			Gln	cag Gln				Pro								1110
		Glu		caa Gln												1158
	Ala			gat Asp												1206

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ta	atggacctt	ttcaatatgc	aaattatgta	atggtacaaa	cgactttata	tcagtataat	673
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C	ctagtggcc	acctctgcca	ttagcctggg	cacttcctgg	gggacagagg	tggaaccccg	853
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Asp Ser Leu Pro Pro Pro Val Phe Ser Glu Gln Val Met Ala Ser Met
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30
35

gct gcc gtg ctc acc tgg gct ctg gct ctt ctt tca gcg ttt tcg gcc 198
Ala Ala Val Leu Thr Trp Ala Leu Ala Leu Ser Ala Phe Ser Ala
40 45 50

acc cag gca cgg aaa ggc ttc tgg gac tac ttc agc cag acc agc ggg
Thr Gln Ala Arg Lys Gly Phe Trp Asp Tyr Phe Ser Gln Thr Ser Gly
55 60 65 70

gac aaa ggc agg gtg gag cag atc cat cag cag aag atg gct cgc gag 294
Asp Lys Gly Arg Val Glu Gln Ile His Gln Gln Lys Met Ala Arg Glu
75 80 85

ccc gcg acc ctg aaa gac agc ctt gag caa gac ctc aac aat atg aac
Pro Ala Thr Leu Lys Asp Ser Leu Glu Gln Asp Leu Asn Asn Met Asn
90 95 100

aag ttc ctg gaa aag ctg agg cct ctg agt ggg agc gag gct cct cgg 390 Lys Phe Leu Glu Lys Leu Arg Pro Leu Ser Gly Ser Glu Ala Pro Arg 105 110 115

ctc cca cag gac ccg gtg ggc atg cgg cag ctg cag gag gag ttg
Leu Pro Gln Asp Pro Val Gly Met Arg Arg Gln Leu Gln Glu Glu Leu
120 125 130 ·

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gttaaggttg ttaatgtaca aaaaaaaaa accettatac tcacetgcgt tttcatttgt 3195

ttgacatttg tctattattg gatatcatta tcatatgaac ttgtcagtgg gaaacaaact 3255

qtctaaaaat ttatctctta cgtttaacat acaatcatgt gagatttagg cagagttcga 3315

taaattactg gcaaaaacaa aactcattta taaagatttt ctaatgttga ctttaatact 3375

3405 ctaacatggt acaaaccana tggtaaaatc

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<211> 902

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (257)..(430)

<400> 188

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337 aga acc cat gta aat ctt tgc tgt ttc tgc cgc tac acc act ccc aag Arg Thr His Val Asn Leu Cys Cys Phe Cys Arg Tyr Thr Thr Pro Lys

atg agt ttc tca tct gca tgt gtg agc ctc tgc tta atg ctg ctg ttt 385 Met Ser Phe Ser Ser Ala Cys Val Ser Leu Cys Leu Met Leu Leu Phe 35

433 tgt tct cct cca ctc ctg ctt ttg ctc ctg tcc tca ttt gtt taa tga Cys Ser Pro Pro Leu Leu Leu Leu Leu Ser Ser Phe Val \* 45 50 55

ctgggttcat ttccttgatc atatttttt ttccttctcc tatttgaatg atgggggcac 493

WO 01/55437				PCT/US01/02623
590	595		600	
_		Ser Arg His S	ct ggg tca ttg gc er Gly Ser Leu Al	•
			gt cag agt acc ag er Gln Ser Thr Se 63	r Arg
			tg ttt tcc gtg ga eu Phe Ser Val Gl 650	
			at atg gca gga gc sp Met Ala Gly Al 665	
		-	tc cct ccc aca ac al Pro Pro Thr Th 680	
		Cys Ala Ser S	cc tca act cag ag er Ser Thr Gln Se 95	
			tg aca agt gtg ga al Thr Ser Val Gl 71	u Pro
Pro Ser Val			ca agt gca ctc ag hr Ser Ala Leu Se 730	
			ca tta gga cga tc hr Leu Gly Arg Se 745	
tcc cta agt Ser Leu Ser 750	cag aac cag agt Gln Asn Gln Ser 755	cct ttg aga c Pro Leu Arg G	aa ctt gat aat gg ln Leu Asp Asn Gl 760	g gta 2427 y Val
		Asp Val Glu M	tg cta att cca at et Leu Ile Pro Il 75	
gat gga tct Asp Gly Ser	tca gac ttt gat Ser Asp Phe Asp 785	gtg aat gac t Val Asn Asp C 790	gc tcc aga cct ct ys Ser Arg Pro Le 79	u Leu
Asp Leu Ala	tca gat caa gga Ser Asp Gln Gly 800	caa ggg ctt a Gln Gly Leu A 805	ga caa cca tat aa rg Gln Pro Tyr As 810	t gca .2571 n Ala
aca aat cct Thr Asn Pro	gga gta agg cca Gly Val Arg Pro	Ser Asn Arg A	at ggc ccc tgt ga sp Gly Pro Cys Gl	g cgc 2619 u Arg

aca ctg aaa aac gaa acg agt gat gat gag gct ttg tta ctt tgt tag Thr Leu Lys Asn Glu Thr Ser Asp Asp Glu Ala Leu Leu Leu Cys  $\star$ 

tgt ggt att gtc cac act gcc cag ata cca gac act tgc tta gaa gta Cys Gly Ile Val His Thr Ala Gln Ile Pro Asp Thr Cys Leu Glu Val

								•				34:	,			
cag Glr	ata Ile 350	: Arg	gta Val	cat His	ttt Phe	tgt Cys 355	Ala	gat a As <u>r</u>	aaa Lys	gtg Val	y aat L Ass 360	ı Ala	gca Ala	agg Arg	g gga g Gly	1227
Phe 365	: Asn	gct Ala	act Thr	tac Tyr	c caa Glr 370	ı Val	a gat L Asp	ggg Gly	tto Phe	tgt Cys 375	Lev	g cca ı Pro	tgg Trp	gaa Glu	ata Ile 380	1275
Pro	tgt Cys	gga Gly	ggt Gly	aac Asn 385	Trp	Gly gag	ı tgt ' Cys	tat	act Thr	Gli	g caq 1 Glr	g cag n Glr	g egt L Arg	tgt Cys 395	gat Asp	1323
GJA aaa	tat Tyr	tgg Trp	Cat His 400	Cys	cca Pro	aat Asn	gga Gly	agg Arg 405	Asp	gaa Glu	aco Thr	aat Asn	tgt Cys 410	Thr	atg Met	1371
Cys	GIn	415	Glu	Glu	Phe	Pro	420	Ser	Arg	Asn	Gly	Val 425	Cys	Tyr	Pro	1419
Arg	3er 430	Asp	Arg	Cys	Asn	435	Gln	Asn		Cys	440	Asn	Gly	Ser	Asp	1467
445	гÀг	Asn	Cys	Phe	Phe 450	Cys	Gln	. Pro		Asn 455	Phe	His	Суѕ	Lys	Asn 460	1515
Asn	Arg	Cys	Val	Phe 465	Glu	Ser	Trp	Val	tgt Cys 470	Asp	Ser	Gln	Asp	Asp 475	Cys	1563
GIŸ	Asp	СТĀ	Ser 480	Asp	Glu	Glu	Asn	Cys 485		Val	Ile	Val	Pro 490	Thr	Arg	1611
vai	TTE	1hr 495	Ala	Ala	Val	Ile	Gly 500	Ser	ctc Leu	Ile	Cys	Gly 505	Leu	Leu	Leu	1659
vai	510	Ala	Leu	Gly	Cys	Thr 515	Cys	Lys	ctt Leu	Tyr	Ser 520	Leu	Arg	Met	Phe	1707
525	Arg	Arg	Ser	Phe	Glu 530	Thr	Gln	Leu	tca Ser	Arg 535	Val	Glu	Ala	Glu	Leu 540	1755
Leu	Arg	Arg	GIU	545	Pro	Pro	Ser	Tyr	gga Gly 550	Gln	Leu	Ile	Ala	Gln 555	Gly	1803
пец	116	PLO	560	vaı	GIu	Asp	Phe	Pro 565	gtt Val	Cys	Ser	Pro	Asn 570	Gln	Ala	1851
Ser	vai	575	GIU	Asn	Leu	Arg	<b>Leu</b> 580	Ala	gta Val	Arg	Ser	Gln 585	Leu	Gly	Phe	1899
act Thr	tca Ser	gtc Val	agg Arg	ctt Leu	cct Pro	atg Met	gca Ala	ggc Gly	aga Arg	tca Ser	agc Ser	aac Asn	att Ile	tgg Trp	aac Asn	1947

80 85 90

			00					03					-			
cag Gln	gat Asp	ttt Phe 95	gat Asp	att Ile	caa Gln	gga Gly	tcc Ser 100	aga Arg	agg Arg	tgc Cys	aat Asn	ttg Leu 105	gac Asp	tgg Trp	ttg Leu	459
aca Thr	ata Ile 110	gaa Glu	aca Thr	tac Tyr	aag Lys	aat Asn 115	att Ile	gaa Glu	agt Ser	tac Tyr	aga Arg 120	gct Ala	tgt Cys	ggt Gly	tcc Ser	507
aca Thr 125	att Ile	cca Pro	cct Pro	ccg Pro	tat Tyr 130	atc Ile	tct Ser	tca Ser	caa Gln	gac Asp 135	cac His	atc Ile	tgg Trp	att Ile	agg Arg 140	555
ttt Phe	cat His	tcg Ser	gat Asp	gac Asp 145	aac Asn	atc Ile	tct Ser	aga Arg	aag Lys 150	ggt Gly	ttc Phe	aga Arg	ctg Leu	gca Ala 155	tat Tyr	603
ttt Phe	tca Ser	GJA aaa	aaa Lys 160	tct Ser	gag Glu	gaa Glu	cca Pro	aat Asn 165	tgt Cys	gct Ala	tgt Cys	gat Asp	cag Gln 170	ttt Phe	cgt Arg	651
					tgt Cys											699
gat Asp	gaa Glu 190	tgt Cys	gga Gly	gat Asp	agt Ser	tcc Ser 195	gat Asp	gaa Glu	gag Glu	atc Ile	tgt Cys 200	gcc Ala	aaa Lys	gaa Glu	gca Ala	747
					gct Ala 210											795
					ttt Phe											843
					aac Asn											891
					aca Thr											939
					aat Asn			-								987
-					gac Asp 290			_		_		_			_	1035
		-			ctt Leu	_						_		_		1083
		_			gag Glu					-		_	-		_	1131
	-		_		cat His	_				-	_					1179

100 105 110

gca ttg aaa gaa tgt cta act gct taa tacct gaaggaaaat atctctgaga 629 Ala Leu Lys Glu Cys Leu Thr Ala \* 115 120 689 cttcctccag ccttgtgatt tgttggatta atataattta actcctagaa agttgagata aatcgtatgg atgataaaaa gctataatga tccagccttt tatgaagaat gcaaaatgga 749 atacctgaag gaaagggaag aattcagaaa aactggaatt cctacaaaga aaaggctaca 809 869 gaagetteca acaageatgt aggeagatac teaaatgaca tteaggaact etaatattea tggaagtcat tttatagtcc ttaaataatg gactcaagca tatatgtttg ctttacctta 929 attatggaaa tattaacttt atctgaaata aatattttat ttgtaaacgc ggccgcgaat 989 teggateete gagagatete tttttttggg tttggtgggg tatetteate gteg 1043

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<211> 3405
<212> DNA
<213> Homo sapiens

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<220>
<221> misc\_feature
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<222> (1)...(3405)
<223> n = a,t,c or g

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cgtcggcgtc gtctacctcc agettetect ecetectect ecgteteete etetetett 120
ccatctgctg tggtt atg gcc tgt ege tgg age aca aaa gag tet eeg egg 171
Met Ala Cha Arg Tro Sor The Luc Clu Cor Bro Arg

60

Met Ala Cys Arg Trp Ser Thr Lys Glu Ser Pro Arg

1 5 10

tgg agg tct gcg ttg ctc ttg ctt ttc ctc gct ggg gtg tac gga aat 219
Trp Arg Ser Ala Leu Leu Leu Leu Phe Leu Ala Gly Val Tyr Gly Asn
15 20 25

ggt gct ctt gca gaa cat tct gaa aat gtg cat att tca gga gtg tca 267 Gly Ala Leu Ala Glu His Ser Glu Asn Val His Ile Ser Gly Val Ser 30 40

act gct tgt gga gag act cca gag caa ata cga gca cca agt ggc ata

Thr Ala Cys Gly Glu Thr Pro Glu Gln Ile Arg Ala Pro Ser Gly Ile

45 50 55 60

atc aca age cca gge tgg cct tct gaa tat cct gca aaa atc aac tgt 363
Ile Thr Ser Pro Gly Trp Pro Ser Glu Tyr Pro Ala Lys Ile Asn Cys
65 70 75

agc tgg ttc ata agg gca aac cca ggc gaa atc att act ata agt ttt 411 Ser Trp Phe İle Arg Ala Asn Pro Gly Glu Ile Ile Thr Ile Ser Phe

aggtgtcaga ctgcaggaaa ggagctcact ctgctgggt ggatatctga ggcagagatc 481
tgctggtata ggggaccaac tggctaagta agtttcccca agactcacgg aatttccaca 541
acaggtgatt taggatctga aaacctgaca attatgggta cacatgaggg gggcagcctg 601
cacaatgttc tccaggtgag gagactggtg gttgagttgc cctttgaaag gggtgggtag 661
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tcccctttct gggcccccgg c 742

<210> 186
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577

aag aac tot gga gtt ott atg gta gta aaa tgo ogg aaa gaa aat tot

Lys Asn Ser Gly Val Leu Met Val Val Lys Cys Arg Lys Glu Asn Ser

PCT/US01/02623 WO 01/55437 Phe Asn Cys Val Ser Pro Gly Ile Leu Pro Ile Ser Leu Cys Leu Ala 253 ttc aat cat gat aga agc acc ttt ttc ttt tca ata ata tta ttg tta Phe Asn His Asp Arg Ser Thr Phe Phe Phe Ser Ile Ile Leu Leu Leu 50 55 302 aaa gcc tta att att ttg tct tct ctg ctt caa act aag taa ttctgac Lys Ala Leu Ile Ile Leu Ser Ser Leu Leu Gln Thr Lys \* 65 362 ttccttaatc ttttatcaca ggctctgttc tccaaacttt cagtcttttc tgttggtcca tattccattq qtttctcctc ctactcattc agaggcaaat taaggtggtt ttttaagttt 422 tggtttgtag actatgtcgt tatgtgagaa atttacttta ggtttgtatt gtcaacccca 482 tagcacaagc caggtactta atttaggcat tagtcagtga tatagattga atatttgtcc 542

602

662 717

<210> 185

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ctgcgcaaat ctcatgttga attgcaatcc ccagtgttgg gggtggcgct tggtggaagg
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<220> <221> CDS

<222> (128)..(361)

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35 40 45

cat caa aga aca agg ctt cta gat gct ctc tgc cca gtc act caa tgc
His Gln Arg Thr Arg Leu Leu Asp Ala Leu Cys Pro Val Thr Gln Cys
50 55 60

cat cac tct gcc tgg ccc tgt gtt tgc cag gga gca cag aca ccc atc

His His Ser Ala Trp Pro Cys Val Cys Gln Gly Ala Gln Thr Pro Ile

65

70

75

tgaggaatcc atgccatgag gagtttatgg tctgtgaaga atacaggcag gaatttgaga 421